UNIVERSITY OF ALBERTA

2,3-ANHYDROFURANOSYL THIOGLYCOSIDES AND SULFOXIDES AS GLYCOSYLATING AGENTS IN THE SYNTHESIS OF α-D-GALACTOFURANOSIDES

by

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Dedicated to my parents and Yujuan

ABSTRACT

Polysaccharides containing α-D-galactofuranosyl residues have been identified in bacteria, fungi, and other lower organisms. However, the stereoselective preparation of α-D-galactofuranosides remains a challenging and unsolved problem.

In this project, we have explored the syntheses of α-D-galactofuranosides via glycosylation of alcohols by 2,3-anhydrofuranosyl thioglycosides and glycosyl sulfoxides, followed by the nucleophilic opening of the epoxide moiety. Three pairs of different protected glycosyl donors, possessing the 2,3-anhydro-D-gulofuranosyl stereochemistry, have been investigated in the glycosylation reactions with various alcohol acceptors. The predominant or exclusive product of reactions with these glycosylating agents is the one in which the newly formed glycosidic bond is *cis* to the epoxide moiety (the α stereochemistry). We also probed the mechanism of the glycosylation reaction with 2,3-anhydrofuranosyl glycosyl sulfoxides via low-temperature NMR spectroscopy.

Finally, we have demonstrated the utility of this methodology through the synthesis of four oligosaccharides containing α-D-galactofuranosyl residues, which are fragments of bacterial or fungal cell wall polysaccharides.

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LIST OF ABBREVIATIONS

Abbreviation	Full Name of Compound
Ac	Acetyl
Ac_2O	Acetic anhydride
aq.	Aqueous
AgOTf	Silver trifluoromethane sulfonate
Bn	Benzyl
BSP	1-benzenesulfinyl piperidine
Bz	Benzoyl
cat.	Catalytic
Cbz	Carbobenzyloxy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropylazodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMTST	Dimethyl(methylthio)sulfonium triflate
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine

Et	Ethyl
IDCP	Iodonium dicollidine pechlorate
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MTr	*p*-Methoxyphenyldiphenylmethyl
NIS	*N*-Iodosuccinimide
Ph	Phenyl
PMB	4-Methoxybenzyl
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tol	Tolyl
Tr	Triphenylmethyl or Trityl
TTBP	2,4,6-tri-*tert*-butyl-pyrimidine

CHAPTER 1

BIOLOGICAL AND CHEMICAL BACKGROUND

1.1 Biological Significance

Oligosaccharides are components of many natural products, and their importance in biological processes, such as immunological responses, molecular recognition, and host-pathogen interactions has been recognized for a long time.[1] Despite recent advances in the structural elucidation of oligosaccharides, the function of many carbohydrates in biological systems remains unknown, because of their complexity.

In common with most biologically active natural products, oligosaccharides can be isolated only in small quantities from natural sources. Moreover, modified analogues of those glycoconjugates are rare or completely absent from nature. The escalating interest in the involvement of carbohydrates, particularly oligosaccharides, in the life sciences, have led to investigations focused not only on further biological studies but also on the chemical or enzymatic synthesis of oligosaccharides, which is the only pathway to access large quantities of molecules required for biochemical research. Successful access to oligosaccharides as well as their modified analogues will enable a better understanding of conformational analysis, carbohydrate-protein interactions[2] (glycosyltransferases and

glycosidases), biosynthetic pathways (*e.g.*, enzymatic synthesis), and carbohydrate-based vaccine development.[3-9]

Synthetic carbohydrate chemistry, especially oligosaccharide construction has historically been a challenge. In 1975, Lemieux and coworkers published the first syntheses of the complex blood group oligosaccharides.[10-13] This series of four papers, which reported the trisaccharide A and B blood group determinants, together with the advent of high field NMR, launched the modern era of carbohydrate synthesis. Since these landmark accomplishments, many methods for the formation of glycosidic linkage have been developed.[14-16] Although it is now generally true that oligosaccharides of various complexity can be assembled, methodologies for the synthesis of oligosaccharides are still not general and reliable enough to always guarantee success. The difficulties of stereo-controlled formation of glycosidic bond at the anomeric centre result in the difficulty and complexity of various oligosaccharide syntheses. This situation can be summarized in the much quoted lines of Hans Paulsen:[17]

"Each oligosaccharide synthesis remains an independent problem, whose resolution requires considerable systematic research and a good deal of know-how. There are no universal reaction conditions for oligosaccharide syntheses."

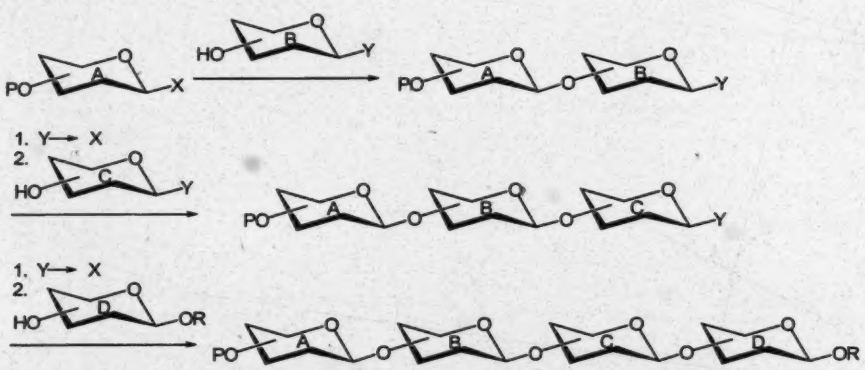
Therefore, the development of new synthetic methods for highly stereoselective glycosidic bond formation remains a worthy pursuit.

1.2 Strategies for Glycosidic Bond Formation

Because oligosaccharides are commonly reached from a combination of several monosaccharide building blocks, the sequence of the construction is the first consideration. Two pathways are possible: linear and convergent. Three different and newly developed methods are also discussed below, including "one-pot" synthesis, enzymetic synthesis, and polymer-supported synthesis.

1.2.1 Linear Synthesis

A linear synthesis is an end-to-end approach that successively connects one monosaccharide to other monosaccharides producing the desired oligosaccharide. In this approach, a protected glycosyl donor is treated with an acceptor to form a disaccharide, followed by the conversion of the anomeric centre at the reducing end to a new glycosyl donor for the next glycosylation. This process is repeated until the final oligosaccharide is built (Figure 1.1).



X represents more reactive aglycon, which can be preferentially activated in presence of Y

Figure 1.1. Linear pathway for oligosaccharide synthesis.

Several modern approaches can be applied to this classical pathway, such as the "orthogonal" method (the selective activation of one donor over another potential donor) and the "armed/disarmed" method (the chemoselective activation of an armed glycosyl donor over a disarmed one, which possesses the same aglycon). The principle of the former method is based on differences in reactivity of the various classes of glycosyl donors. This method is prevalent and there are many successful examples over years.[18-21] In the latter method, two potential glycosyl donors possessing the same aglycon functionality are used. One, the "armed" species serves as the donor while the other, the "disarmed" species is the acceptor. A glycosyl donor is normally "armed" by the electron-donating protecting groups such as benzyl groups. In contrast, "disarmed" glycosides are usually functioned with electron-withdrawing protection like benzoyl and acetyl groups.

1.2.2 Convergent Synthesis

A convergent synthesis is a block-by-block connection method, which assembles the oligosaccharide from several smaller saccharide pieces (Figure 1.2). The advantage of a convergent synthesis is that most of the chemistry has been carried out on smaller components and thus fewer manipulations need to be performed on the large oligosaccharide. Moreover, expensive and difficult-to-synthesize building blocks can be introduced late in the synthetic sequence to minimize the expense and effort. The

"orthogonal" and "armed/disarmed" approaches are widespread in the convergent approach as well.

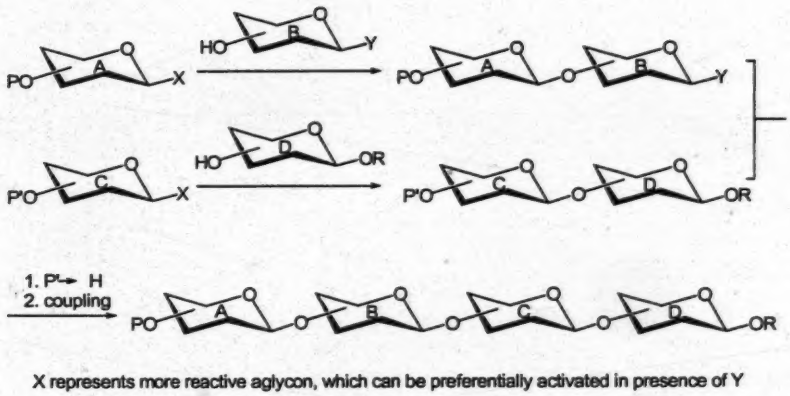


Figure 1.2. Convergent pathway for oligosaccharide synthesis.

1.2.3 "One-pot" Synthesis

The concept of "one-pot" oligosaccharide synthesis was first introduced by Takahashi[22] and further developed by other chemists including Ley,[23] Wong,[24, 25] and Huang[26] (Figure 1.3). Obviously, the one-pot approach is a dream method and the ultimate goal for synthetic carbohydrate chemists. This method allows a chemist to build a molecule without manipulation of protecting groups, and also skips many tedious purification processes by saving steps. In 1999, Wong and coworkers described "programmable, one-pot oligosaccharide synthesis".[24] Recently, study in this area has been very popular and notable strides have been made.[23-28] However, the development of

one-pot synthesis is only starting and not universal because there are many aspects that must be further developed and optimized.

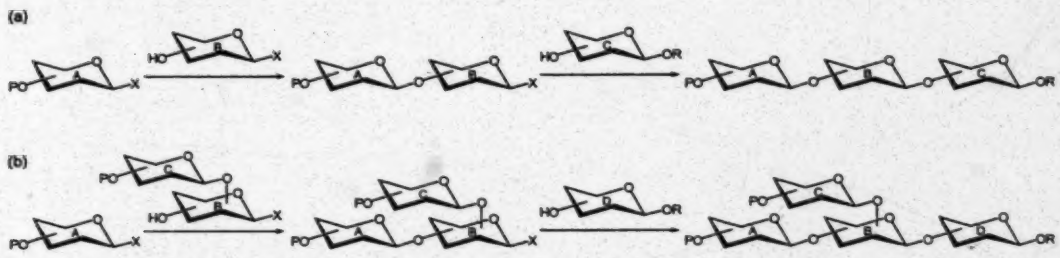


Figure 1.3. "One-pot" pathway for oligosaccharide synthesis. (a) A linear trisaccharide synthesis; (b) A convergent tetrasaccharide synthesis.

1.2.4 Polymer-Supported Synthesis

Classical chemical methods for oligosaccharide synthesis invariably require extensive purification of the reaction products, mostly by chromatography, which makes this approach very laborious and expensive. Similar problems are also encountered in the one-pot synthesis approach as well, but are minimized. Polymer-supported oligosaccharide synthesis facilitates quick and efficient purification, assuming that all reactions proceed to completion. The primary purpose of this approach is the rapid and easy purification of the polymer-supported product after each step in the reaction sequence leading to the formation of an oligosaccharide.[29] Therefore, polymer-supported synthesis does not decrease the number of steps, but makes the process enormously faster (Figure 1.4).

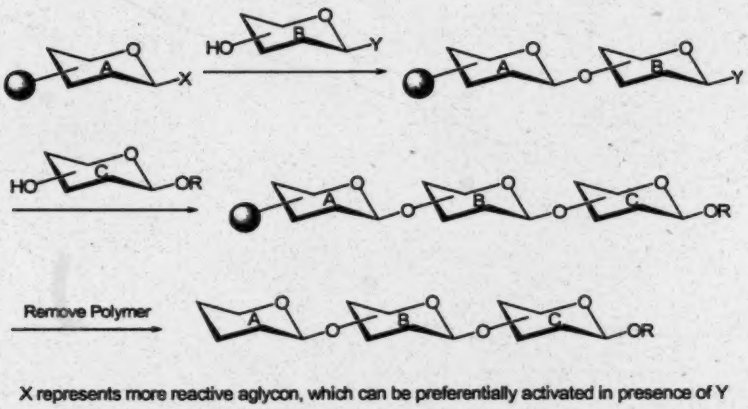


Figure 1.4. Polymer-supported pathway for oligosaccharide synthesis.

Furthermore, for combinatorial synthesis of oligosaccharide libraries,[30] the polymer support is essential because it allows purification of the desired intermediates or products as groups, which is extremely difficult to accomplish using solution methods.

1.2.5 Enzymatic Synthesis

A number of enzymes in nature are associated with the processing of carbohydrates, carrying out reactions such as glycosylation, isomerization, oxidation, reduction, dehydration, phosphorylation, and carbon-carbon bond formation. Among them, glycosyltransferases are useful and important in the construction of glycosidic linkages, and are responsible for the polymerization of monosaccharides into polysaccharides, and the synthesis of complex oligosaccharides. The advantage of enzymatic synthesis is the

high regio and stereoselectivity exhibited by enzymes; however the cost, accessibility and specificity of enzymes sometimes limits the use of this approach (Figure 1.5).[31]

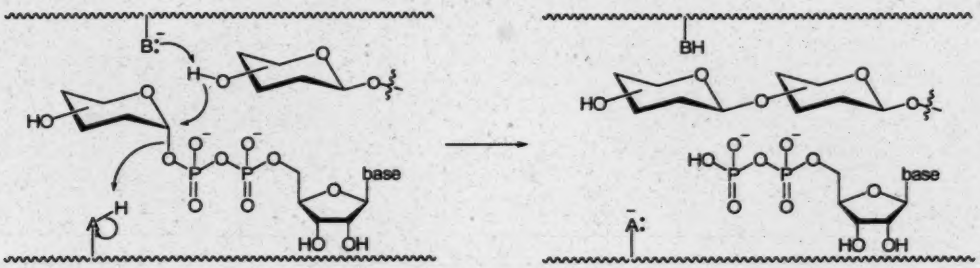


Figure 1.5. Enzymatic pathway for oligosaccharide synthesis.

1.3 Chemical Synthesis of Glycosidic Linkages

In the classic chemical strategies, the overwhelming majority of glycoside syntheses involve an ionic mechanism. In general, three types of strategies are outlined (Figure 1.6).

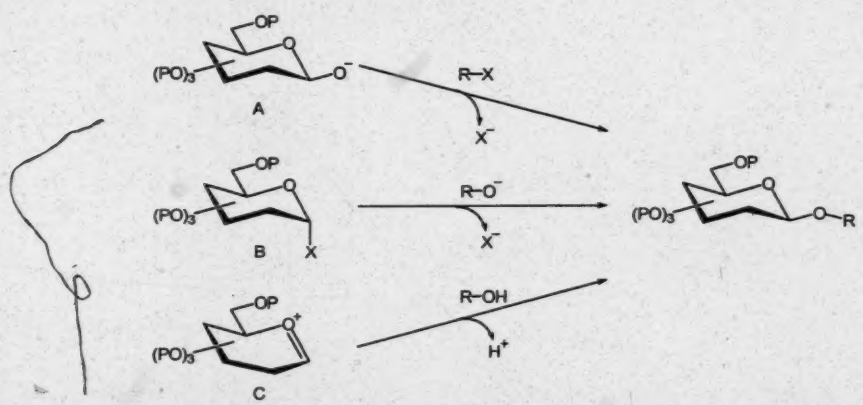


Figure 1.6. Possible routes for formation of glycosidic linkages based on ionic mechanism. a) Alkylation of glycosyl alkoxides via an S_N2 reaction; b) S_N2 displacement of glycosyl halides with aglyconic alkoxides; c) Trapping of glycosyl electrophiles with nucleophiles.

Alkylation of glycosyl alkoxides via an S_N2 reaction[32, 33] is mostly employed in the preparation of glycosides of simple alcohols. With a reactive leaving group installed on aglycone alcohols (*e.g.*, triflate), glycosyl alkoxides readily react via an S_N2 pathway to produce glycosides, sometimes with good stereoselectivity. However, this selectivity is difficult to predict and relies on the polarity of the solvent, the reaction temperature, and the sugar substrate. This strategy has been applied to the oligosaccharide preparation as well, but only a few successful examples have been reported (*e.g.*, Figure 1.7).[34]

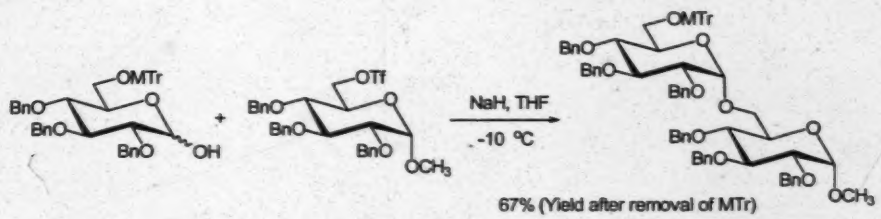


Figure 1.7. Glycosylation via alkylation of glycosyl alkoxides.

S_N2 displacement of glycosyl halides with aglyconic alkoxides is a suitable option to stereoselectively prepare only *O*-aryl glycosides and thioglycosides.[35-37] Because of the strong basicity of alkyl alkoxides, side reactions, especially elimination, are often observed and thus this approach is of limited use (Figure 1.8).

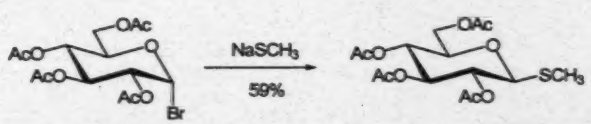


Figure 1.8. Glycosylation via S_N2 displacement of glycosyl halides

Trapping of glycosyl electrophiles with nucleophiles is the most popular and frequently used strategy.[17, 32, 38] A number of the glycosyl donors have been developed, with various activatable groups at the anomeric position. The differences between these groups are mostly focused on the diverse activation methods and activation rates. Some donors work better in some cases than others and vice versa. The reactivities of glycosyl donors are associated with many factors, such as differences in protecting groups, substituents on both sugar and aglycon, and the stereochemistry of the sugar. Most reactivity trends can be rationalized by electronic effects, which determine the stability of the oxocarbenium intermediate. Although the influences of the acceptor and solvent on the rate of the glycosidic bond formation have been less investigated, general trends indicate that hydroxyl groups between bulky protecting groups are less reactive, and that glycosylation reactions are favored in aprotic solvents of moderate polarity (*e.g.*, CH_2Cl_2, CH_3NO_2). Because of the wide usage of glycosidic syntheses, this strategy remains an active area of research (Figure 1.9).

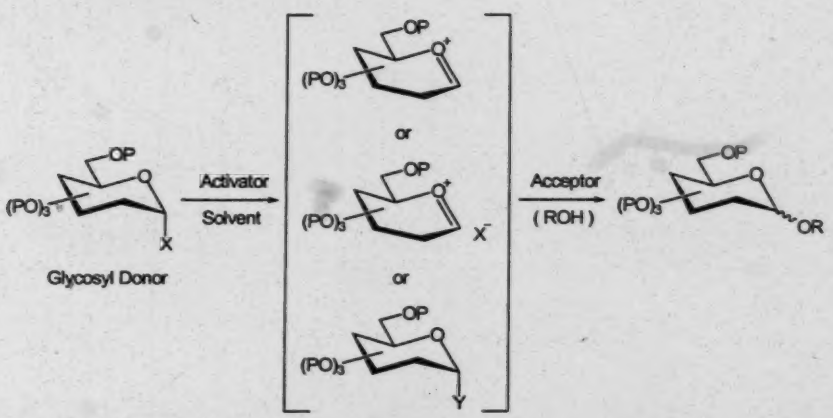


Figure 1.9. General mechanism of trapping glycosyl electrophiles with nucleophiles.

1.4 Regioselectivity and Stereoselectivity of Glycosylation Reactions

The key to success of any glycosylation reaction involves control of regioselectivity and stereoselectivity. Both have been a big concern when chemists are developing new glycosylation methods.

1.4.1 Regioselectivity of Glycosylation Reactions

Obviously, regiocontrol is never a concern when simple alcohols are glycosylated. For sugar acceptors with more than one hydroxyl group, regioselectivity in a glycosylation reaction is generally achieved by the selective protection of hydroxyl groups. However, in some cases, good regiocontrol has been observed in the absence of protecting groups, which is usually based on huge differences in reactivity of the hydroxyl groups (Figure 1.10).[39]

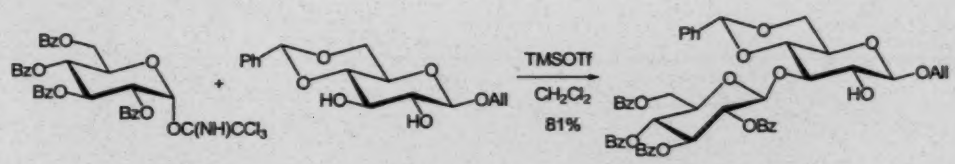


Figure 1.10. Regioselective glycosylation of 4,6-benzylidenated glucopyranosides.

1.4.2 Stereoselectivity of Glycosylation Reactions

Compared to regioselectivity, stereocontrol in a glycosylation reaction is much more complicated and difficult to realize. The stereoselectivity usually depends on many

factors, including the protecting group next to the anomeric centre in a glycosyl donor, the anomeric effect, the configuration of the donor and acceptor, and the solvent.

In general, activation of donors with *O*-acyl or *N*-acyl groups next to the anomeric centre leads to 1,2-*trans* products (both α and β). Neighboring group participation of the acyl group provides a stable dioxolenium ion intermediate, which favors the acceptor's attack from the opposite face to give directly *trans* glycosides (Figure 1.9). Nevertheless, stereochemical control may decrease if the substituent of the acyl moiety is a strong electron withdrawing group, which consequently reduces the ability of the acyl group to participate.

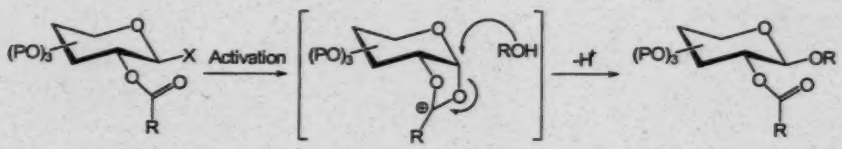


Figure 1.11. General C-2 *O*-acyl group participating pathway.

In contrast, the presence of non-acyl protecting groups at C-2 often means a lack of stereochemical certainty. Typical examples of non-participating groups are hydrogen, azide, and most commonly, alkoxy groups. In such cases, the outcome depends more heavily on the method of activation and the reaction conditions. It has been proposed that in many cases a naked oxocarbenium ion or an ion pair is the transient intermediate and the major product is formed via the kinetic anomeric effect.[40-42]

Solvent effect on stereoselectivity has also been studied, but not to a large degree. A representative example is the use of acetonitrile as a solvent in the synthesis of α-sialosides (Figure 1.12).[43-45] The selectivity of this reaction was suggested to proceed through a β-nitrilium ion, followed by the S_N2 displacment by the acceptor. An α-D-glucosyl nitrilium ion derivative has been detected,[46] which confirms the use of acetonitrile as a solvent to increase the equatorial selectivity. On the contrary, ethers can be used as solvents or co-solvents to increase axial selectivity,[47-49] but the origin of this effect is unclear.

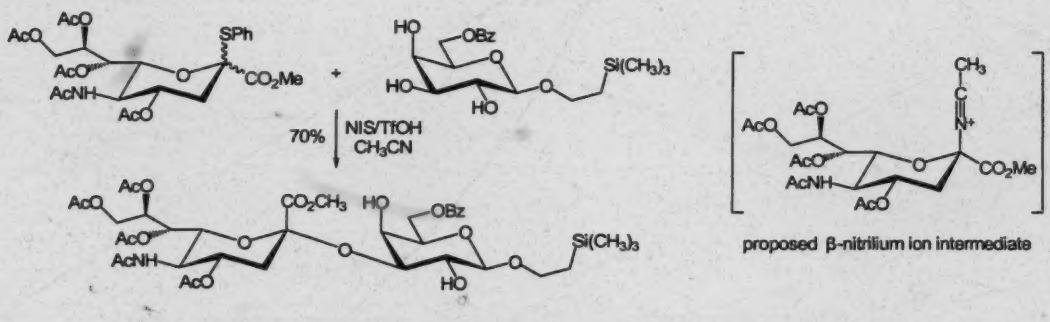


Figure 1.12. Solvent effect in the synthesis of sialic acid.

1.5 Types of Glycosyl Donors

In the last thirty years, carbohydrate chemists have developed many different types of glycosyl donors,[16, 50] each having its own advantages and disadvantages. However, all of them have two essential features: 1) the substituent at the anomeric centre of the

glycosyl acceptor must remain unaffected by the activation conditions; 2) any other existing glycosyl linkages must also be unaffected by the activation process.

1.5.1 Glycosyl Bromides

Glycosyl bromides were the first glycosyl donors to be used for disaccharide formation by Koenigs and Knorr[51] in their classical glycosylation reaction at the turn of the twentieth century. Activation of bromides involves reactions with silver (AgOTf, Ag_2O) or mercury ($HgBr_2$) salts. The reaction probably proceeds via an S_N1 type pathway through the formation of oxocarbenium ion intermediate (Figure 1.13). Although they were the first example of glycosyl donors, glycosyl bromides are still used to some degree, but less than other donors because they are not particularly stable—they are often generated and used *in situ* for glycosylation.

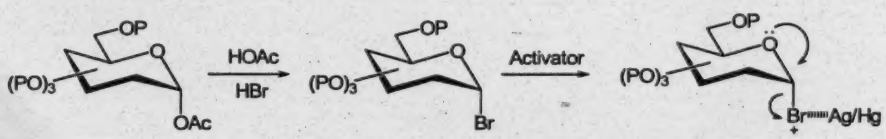


Figure 1.13. Formation and activation of glycosyl bromides.

1.5.2 Thioglycosides

Thioglycosides, where a sulfur atom replaces the oxygen of the aglycon, are a powerful class of glycosyl donors. They are readily prepared from the corresponding anomeric acetates by treatment with a thiol and a Lewis acid. Thioglycosides have the

advantage over glycosyl bromides that they are more hydrolytically stable, and can only be activated under specific reaction conditions. Activation of thioglycosides can be achieved by many promoters, including *N*-iodosuccinimide (NIS) and silver triflate (AgOTf),[52] iodine dicollidine perchlorate (IDCP),[53] dimethyl(methylthio)sulfonium triflate (DMTST),[54] 1-benzenesulfinyl piperidine (BSP) and triflic anhydride (Tf_2O),[55] among others (Figure 1.14). These activation methods are particularly selective and do not affect either the existing glycosidic linkage or most protecting groups. Thioglycosides can be easily converted to other types of donors if necessary (see later, Figure 1.20).

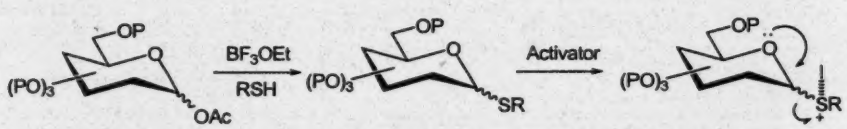


Figure 1.14. Formation and activation of thioglycosides.

1.5.3 Trichloroacetimidates

Trichloroacetimidates were introduced by Sinaÿ[56] and well established by Schmidt[34] to rival other glycosylation methods. Depending on the type of base used, either the α- or β- trichloroacetimidate may be easily prepared from the reducing sugar. The use of potassium carbonate favors the formation of the kinetic product, the β-anomer, whereas sodium hydride favors the thermodynamic product, the α-anomer.

Activation of anomeric trichloroacetimidates is usually achieved by treatment with a Lewis acid (*e.g.*, TMSOTf, $BF_3{\cdot}OEt_2$, and others, Figure 1.15).

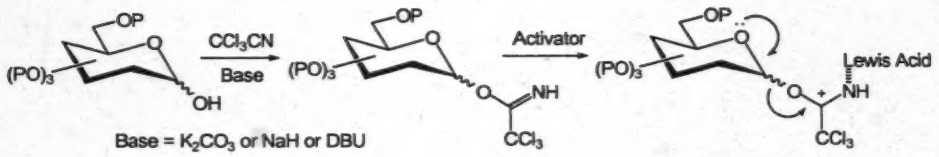


Figure 1.15. Formation and activation of trichloroacetimidates.

1.5.4 Glycosyl Fluorides

Glycosyl fluorides are readily synthesized from either thioglycosides or reducing sugars by treatment with diethylaminosulfur trifluoride (DAST, Et_2NSF_3). Glycosyl fluorides are much more stable than the corresponding bromides or chlorides, and often even inert to many reaction conditions. Therefore, they were not recognized as glycosyl donors until about 1980, when Mukaiyama introduced a range of promoters to activate glycosyl fluorides.[57, 58] Later, Nicolaou further developed this method by converting thioglycosides into fluorides[59] for subsequent use as a glycosyl donor in the synthesis of oligosaccharides.

Activation of fluorides can be performed by the addition of hard Lewis acids such as $BF_3{\cdot}OEt_2$ or $SnCl_2$. Selective activation can be achieved with a number of fluorophilic promoters (*e.g.*, Cp_2HfCl_2). Glycosyl fluorides can generally be used in the synthesis of both 1,2-*cis* and 1,2-*trans* glycosides. In practice, the outcome still depends on the neighboring group at C-2 and the choice of reaction solvents (Figure 1.16).

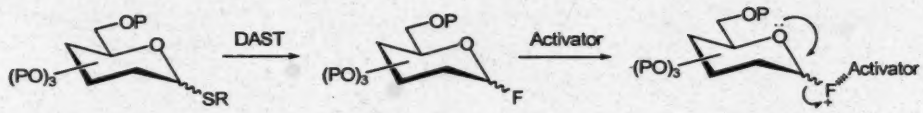


Figure 1.16. Formation and activation of glycosyl fluorides.

1.5.5 Glycals

Although Ferrier[60] discovered the transformation of glycals to glycosides in the presence of a Lewis acid and a reactive alcohol in 1969, it was not until twenty years later, when Danishefsky established this as an efficient method for oligosaccharide synthesis.[14] Treatment of a glycal with dimethyl dioxirane installs the epoxide selectively from the less hindered face to form 1,2-anhydrosugar, which readily acts as a donor with suitable glycosyl acceptors upon treatment with catalytic amount of a Lewis acid (*e.g.*, $ZnCl_2$). Obviously, the glycosylation process goes through a S_N2 pathway and thus gives the 1,2-*trans* glycoside (Figure 1.17). This method is especially powerful for the preparation of glycosides with free 2-OH group that can be used for further manipulation.

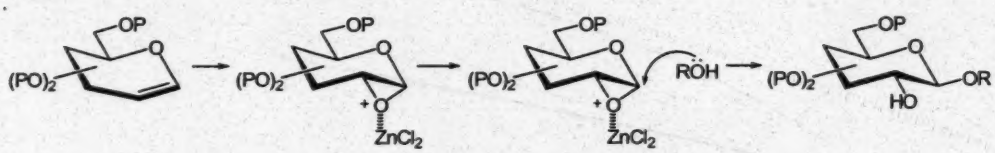


Figure 1.17. Glycosylation of glycal epoxides.

Gin introduced the direct oxidative addition to glycals to extend the use of glycals as potential donors.[61-63] This improvement does not require formation of glycal epoxide in a

separate step. More importantly, both isomeric epoxides can be selectively prepared via the use of different oxidative reagents, leading to the formation of different sugar configurations (Figure 1.18).

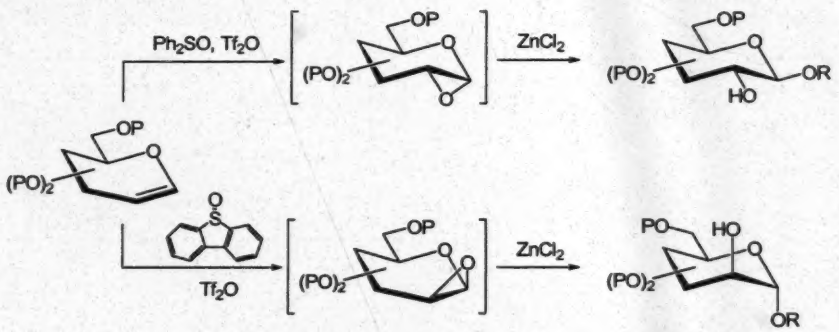


Figure 1.18. Gin's direct oxidative addition to glycols.

1.5.6 Glycosyl Sulfoxides

Glycosyl sulfoxides[64] are easily synthesized by oxidation of thioglycosides with a number of oxidizing reagents, such as *m*-chloroperbenzoic acid (*m*-CPBA). Most of them are hydrolytically stable and can be stored. Activation involves the use of triflic anhydride (Tf_2O) as the promoter, and the addition of a hindered base (*e.g.*, DTBMP, TTBP[65]) to reduce the acidity of the reaction (Figure 1.19). The strength of the method is that some very unreactive acceptors may be glycosylated under very mild conditions. In some cases, the reactions even proceed at -100 °C.

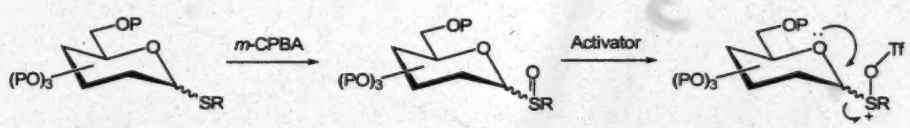


Figure 1.19. Formation and activation of glycosyl sulfoxides.

The donors described above are only several of the most popular glycosyl donors in contemporary carbohydrate syntheses. Other useful derivatives include glycosyl phosphates (Wong),[66] *n*-pentenyl glycosides (Fraser-Reid),[67] glycosyl acetates,[68] seleno glycosides (Pinto),[69] and *in situ* activation of hydroxyl groups (Gin).[70-72] Most of these donors can be generated from thioglycosides directly or indirectly (Figure 1.20).

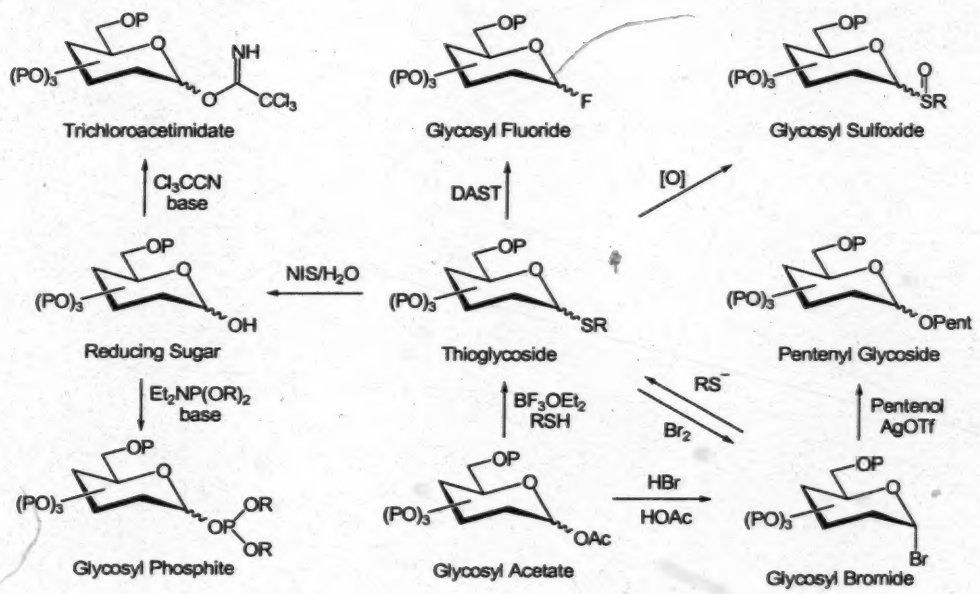


Figure 1.20. Interconversion of different types of glycosyl donors.

1.6 Synthesis of Furanosyl Glycosides

Polysaccharides containing sugar residues in the furanose ring form are significant glycoconjugates in many lower organisms including bacteria,[73, 74] parasites,[75] and fungi.[76]

The structures of many of the furanose-containing glycoconjugates have been identified comparatively recently, in which polysaccharides containing arabinofuranose (Ara*f*), galactofuranose (Gal*f*) or fructofuranose (Fru*f*) are the most widespread in nature (Figure 1.21). Due to the increasing focus on the biological investigations of bacterial cell wall structures for potential treatment of diseases, efficient synthetic methods are urgently needed to provide large amount of furanose-containing oligosaccharides. This area has drawn more and more attention of chemists.

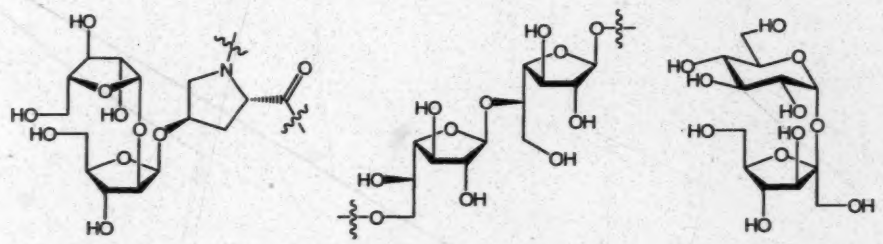


Figure 1.21. Examples of polysaccharides containing (a) Ara*f* (b) Gal*f* (c) Fru*f* residues.

1.6.1 Synthesis of *trans*-Furanosides

The stereocontrolled preparation of 1,2-*trans* furanosides can be straightforwardly achieved through the use of glycosyl donors possessing acyl-protected neighboring groups. Upon activation of the donor, neighboring group participation of the acyl group ensures that the predominant products of the reactions are those in which the glycosidic bond is trans to the acyl substituent (1,2-*trans* glycoside). Several successful syntheses of oligofuranosides with *trans* glycosidic linkages have been reported over the past few

years,[77, 78] including oligosaccharide fragments of mycobacterial arabinogalactan,[79-81] and a structural motif in a *Trypanasoma cruzi* glycosylinisitolphospholipid (Figure 1.22).[82] Similar to the syntheses of pyranosides, the most popular donors have been thioglycosides, *n*-pentenyl glycosides, and trichloroacetimidates; however, the use of other donors has been reported as well.[83, 84]

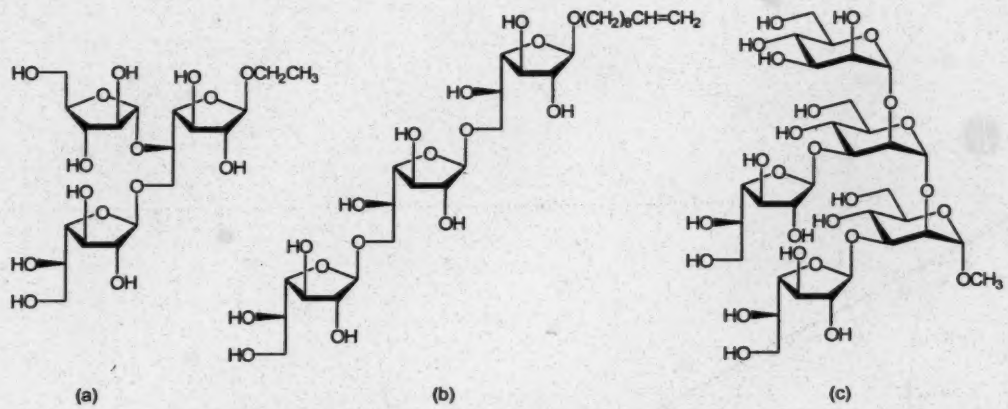


Figure 1.22. Examples of synthesized furanose-containing oligosaccharides. (a and b) Fragments of mycobacterial arabinogalactan; (c) A structural motif in *T. cruzi*.

1.6.2 Synthesis of *cis*-Furanosides

By contrast, the stereoselective synthesis of 1,2-*cis* furanosyl glycosides is considerably more challenging. The stereoelectronic effects that can be exploited to produce good yields of 1,2-*cis* pyranosides, are attenuated because of the comparatively flexible conformation of furanosides. The problems in the preparation of these glycosidic bonds are therefore analogous to those encountered in the synthesis of β-mannopyranosides.[85] The use of donors with nonparticipating (*e.g.*, benzyl) protecting

groups on C-2 (C-3 in Fru*f*), in general, leads to mixtures of products.[86, 87] Although in some cases the reaction conditions can be optimized to provide good yields of the 1,2-*cis* furanosides,[88, 89] these methods do not always work well. These difficulties have, in recent years, led to the development of new methods for the installation of these residues into oligosaccharides.

1.6.2.1 Molecular Tethering—intramolecular aglycon delivery (IAD)

Of all the potential solutions to synthesize biologically important β-mannopyranosides, a particularly elegant idea is to introduce the glycosidic bond intramolecularly by temporarily linking the donor and the acceptor in advance.

First reported by Hindsgaul,[90-92] and later modified by Stork,[93] and then Ogawa and Ito,[94, 95] these methods tether an alcohol at C-2 and then have it trap the developing oxocarbenium to give the desired β-mannopyranoside linkage in a stereoselective manner. The differences between methods involve the use of different tethered intermediates, including a carbon tether (Hindsgaul), silicon tether (Stork), and methoxybenzylidene acetal tether (Ogawa and Ito). Similar approaches have been used for the stereoselective formation of α-glucopyranosides and α-galactopyranosides containing disaccharides.[96]

Oscarson and co-workers applied the IAD approach to the synthesis of furanosides as well.[97] Their successful extension of this method to the stereoselective synthesis of β-D-fructofuranosides broadens the usage of intramolecular aglycon delivery approach in synthetic carbohydrate chemistry (Figure 1.23).

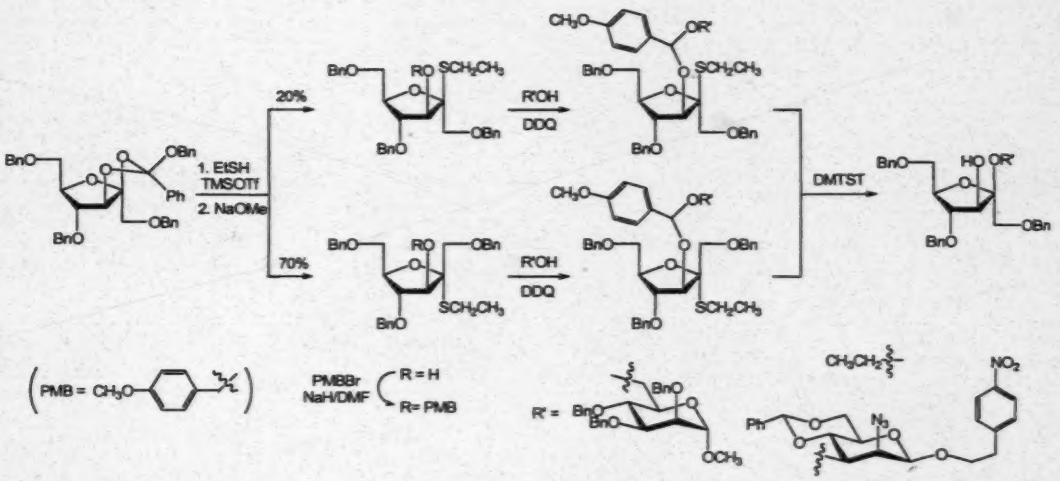


Figure 1.23. Stereospecific synthesis of *β*-D-fru*f* using thioglycoside donors via IAD.

Prandi and co-workers have applied the intramolecular aglycon delivery method to the preparation of a pentasaccharide[87] formed in the mycobacterial cell wall (Figure 1.24). In a key two-step transformation, both β-Ara*f* residues were installed simultaneously with

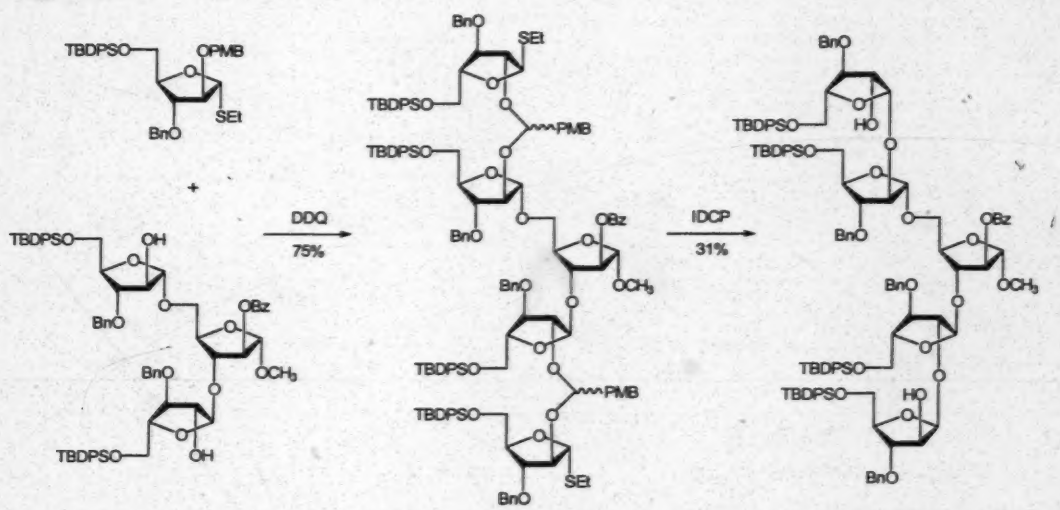


Figure 1.24. Stereoselective synthesis of *β*-D-Ara*f* pentasaccharide via IAD.

complete stereoselectivity through the coupling of trisaccharide with an excess of thioglycoside. This approach has been used to synthesize other β-arabinofuranosides.[99]

Recently, the similar method was used by Ferrières and co-workers[100] for the synthesis of α-D-fucofuranosides (6-deoxy-α-D-galactofuranosides). The ultimate goal of this work is the synthesis of the hexasaccharide repeating unit of the cell surface polysaccharide generated by *Eubacterium saburreum* T19,[101] which is a nonsporing, Gram-positive, and obligately anaerobic rod that inhabits the human mouth (Figure 1.25).

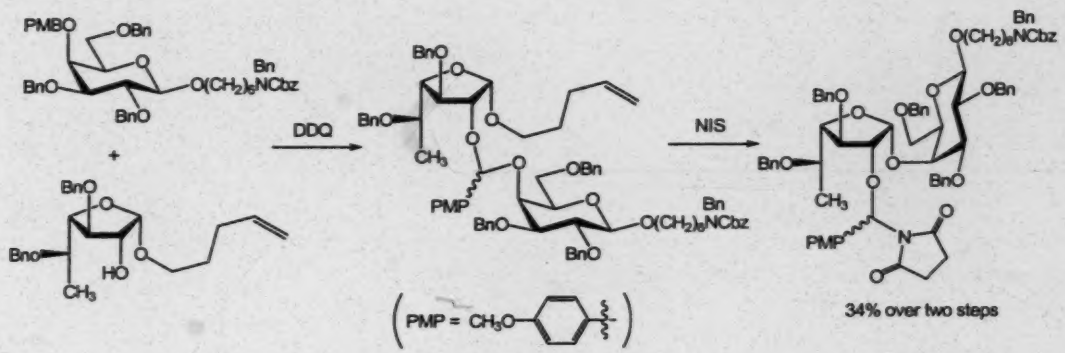


Figure 1.25. IAD synthesis of α-D-fucofuranose-containing disaccharides.

1.6.2.2 A Novel β-Directing Fructofuranosyl Donor Concept

Although the IAD method enabled the synthesis of several β-fructofuranosides, it was not successful in the preparation of sucrose. Thus, Oscarson and co-workers[102] developed a new glycosyl donor (Figure 1.26), in which the siloxane protecting group on the bottom face of the furanose ring prohibits the formation of the α-glycoside and thus

result to the β-glycoside in excellent yield. This method has both been used for the preparation of sucrose as well as the first synthesis of fragments of levan and inulin.[103]

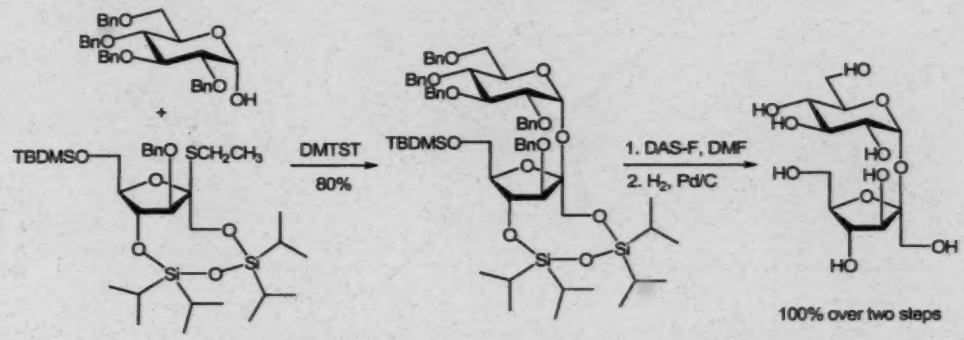


Figure 1.26. Synthesis of sucrose: a novel β-directing fructofuranosyl donor concept.

1.6.2.3 Synthesis via 2,3-Anhydrosugars

A highly stereoselective synthesis of β-arabinofuranosides via 2,3-anhydrofuranosyl donors has been reported by Lowary and co-workers.[104] This two-step protocol involves first the glycosylation of an alcohol with a 2,3-anhydro glycosyl donor, and then the regioselective opening of epoxide moiety with a nucleophile.

This approach was investigated using both thioglycoside and sulfoxide donors, which are readily prepared in two consecutive steps in high yield (Figure 1.27). By protecting the hydroxyl groups at C-2 and C-3 as an epoxide, these species constitute a

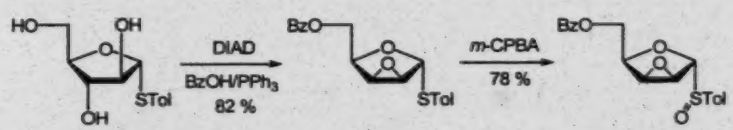


Figure 1.27. Synthesis of thioglycoside and sulfoxide 2,3-anhydrolyxofuranosyl donors.

fundamentally new class of glycosylating agent. The epoxide can be viewed as a nonparticipating C-2 protecting group, differing from all other non-participating oxygen protecting groups in that they are not sterically demanding.

A number of alcohols were glycosylated with these 2,3-anhydrosugar donors. The glycosylation reactions with sulfoxide donors are highly stereocontrolled, leading to the β-glycoside as the major, and often only, product. Recent investigations[105] on the mechanism of these glycosylation reactions suggest that glycosyl triflates are formed *in situ* and that this triflate intermediate is a key to the observed high stereocontrol (Figure 1.28). The corresponding thioglycoside donors gave similar results when activated with *N*-iodosuccinimide. However the underlying factors leading to the reaction stereoselectivity with thioglycoside donors are unknown due to lack of mechanistic investigation.

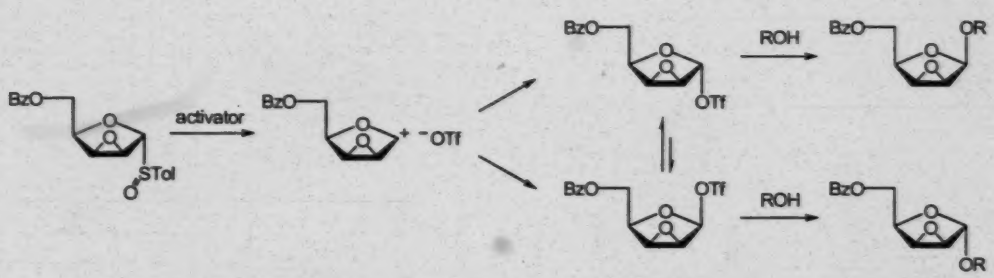


Figure 1.28. Postulated mechanism of glycosylation reaction via sulfoxide donor.

In the second step, the epoxy glycoside product is opened with a nucleophile (*e.g.*, BnOLi) regioselectively at C-3 to provide β-arabinofuranosides. It was discovered that the opening of the epoxide can be made to proceed with high regiocontrol if the reaction

is carried out using lithium alkoxide in the presence of (-)-sparteine (Figure 1.29). The reasons for the observed regioselectivity in these reactions are unknown and are currently under investigation.

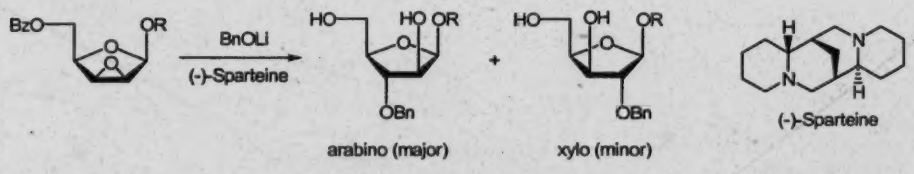


Figure 1.29. Epoxide ring opening with lithium benzylate and (-)-sparteine.

Although the method involves two separate steps, the overall transformation yields of this methodology are comparable to other routes for the preparation of β-arabinofuranosides.[98] In addition to its use for the preparation of *O*-glycosides, this glycosylation method can also be extended for the synthesis of 2,3-anhydrosugar nucleoside derivatives.[106]

1.7 Reseach Goal

Polysaccharides containing α- and β-D-galactofuranosyl residues are widespread in bacteria, fungi,[76, 107] parasites,[75] and other lower organisms. Although β-galacto-furanosides can be accessed through the use of 2-*O*-acylated glycosyl donors,[108-111] the stereoselective preparation of α-D-galactofuranosides remains a challenging and unsolved problem. Current methods used are either low yielding or poorly selective. Toward this end, we are investigating the syntheses of α-D-galactofuranosides via 2,3-anhydro-

furanosyl thioglycoside and glycosyl sulfoxide donors, in which the hydroxyl groups at C-2 and C-3 are "protected" as an epoxide, followed by the regioselective epoxide ring opening. These donors have the 2,3-anhydro-D-gulofuranosyl stereochemistry (Figure 1.30).

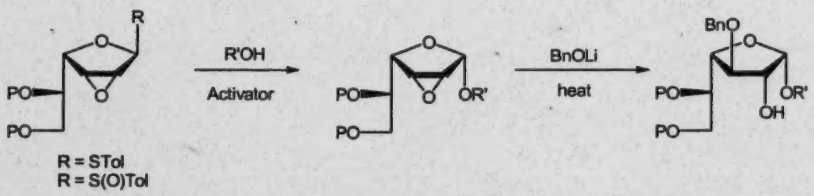


Figure 1.30. General scheme for glycosylation via 2,3-anhydro-D-gulofuranosyl donors.

After the method was developed, it was applied to syntheses of oligosaccharides with α-D-galactofuranosyl residues (Figure 1.31), which are fragments of bacterial or fungal cell wall polysaccharides.[101, 107, 112, 113]

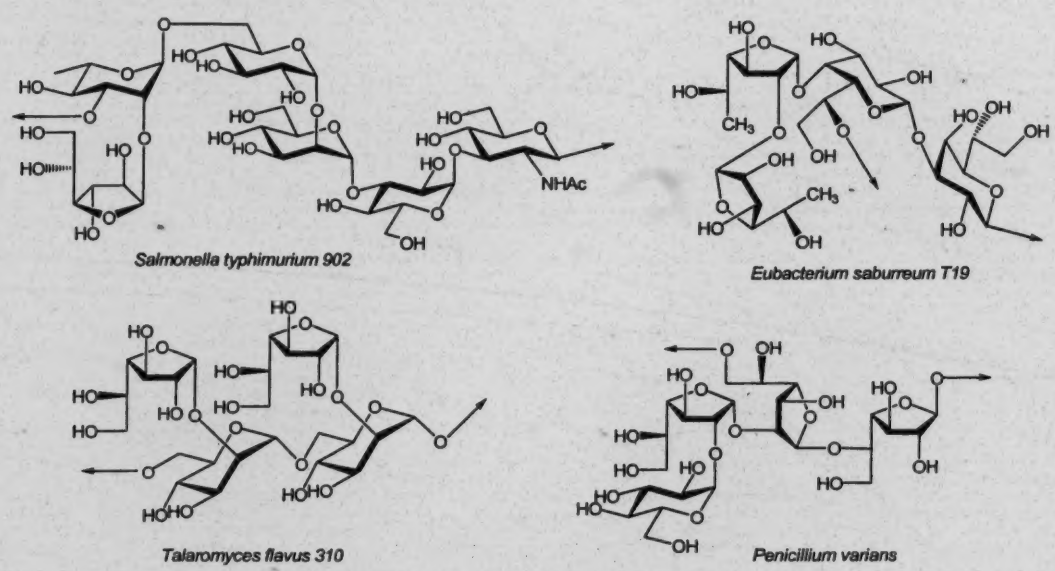


Figure 1.31. Polysaccharides containing α-D-galactofuranosyl residues.

CHAPTER 2

SYNTHESIS OF α-D-GALACTOFURANOSIDES VIA 2,3-ANHYDROSUGARS. METHODOLOGY DEVELOPMENT

2.1 Project Aims

Previous success in the synthesis of β-D-arabinofuranosides via 2,3-anhydor sugars from our laboratory[104] suggests that glycosyl donors possessing the 2,3-anhydro-D-*gulo* stereochemistry will be converted in high yield to the corresponding α-D-galacto-furanosides via epoxy glycosides. The specific aims of this project are:

Specific Aim 1. To explore the use of glycosyl donors with the 2,3-anhydro-D-*gulo* stereochemistry for the synthesis of α-D-galactofuranosides;

Specific Aim 2. To apply the method to the synthesis of natural products containing α-D-galactofuranoside moieties;

Specific Aim 3. To probe the mechanism of these glycosylation reactions through the combined use of NMR spectroscopy and computational chemistry.

2.2 Synthesis of 2,3-Anhydro-D-gulofuranosyl Donors

As discussed in the previous chapter, donors possessing different protecting groups can result in variations in the stereoselectivity of glycosylation reactions. In addition,

previous experience suggested that the different protective groups may affect the regioselectivity of epoxide opening reactions as well. Therefore, donors with different protecting groups were prepared for exploring the issue of regio- and stereoselectivities in these reactions (Figure 2.1).

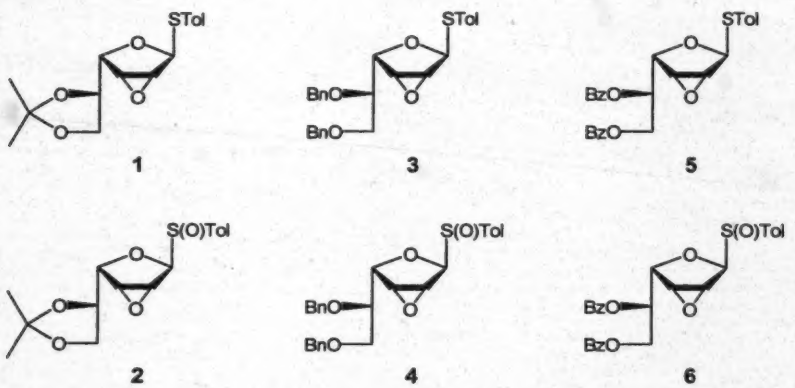


Figure 2.1. Target 2,3-anhydrosugar donors for investigation in glycosylation reactions.

2.2.1 Synthesis of 5,6-*O*-isopropylidene Donors

Several methods have been reported to convert D-galactose to its furanoside form, but most of them are low yielding and the desired furanosides are often difficult to separate from the isomeric pyranosides. We chose to prepare donor **1** through the conversion of commercially available D-galactose to its corresponding diethyl dithioacetal **7**, which can be purified by recrystallization from ethanol.[114] Earlier reports showed that removal of dithioacetal groups under mild conditions (I_2 and CH_3OH) led to the formation of corresponding methyl furanosides in good yield for D-arabinose,

D-glucose, and D-mannose dithioacetals.[115] However, the reaction was not reported for D-galactose. Therefore, a similar reaction was investigated in our group for D-galactose diethylthioacetal. A high yielding and exclusive formation of methyl D-galacto-furanosides from dithioacetal **7** was accomplished using 5% iodine solution in methanol. Classical acetylation[116] of the aforementioned intermediate with acetic anhydride in pyridine gave tetra-*O*-acetylated derivative **8** in 85% yield over two steps after purification (Figure 2.2).

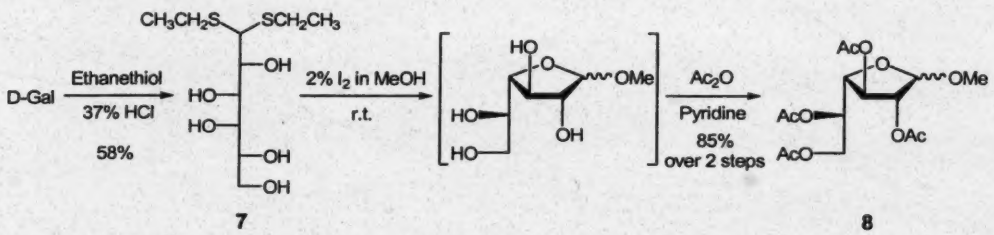


Figure 2.2. An efficient method for formation of methyl D-galactofuranoside.

A wide variety of methods[117] have been developed for the preparation of thio glycopyranosides. However, few precedents on the synthesis of thio glycofuranosides have been reported.[118, 119] Typical methods involve the reaction of a peracylated sugar with a thiol and a Lewis acid, or the transformation of a methyl glycoside to a thioglycoside under similar conditions. Treatment of compound **8** with thiocresol and $BF_3 \cdot OEt_2$ in dichloromethane gave a mixture of α and β thioglycoside **9** in good yield. Owing to the participation of the acyl group at C-2, the major product obtained possesses the β-configuration, which was confirmed by the coupling constant ($^3J_{H\text{-}1,\,H\text{-}2}$ = 2.5 Hz) in

the ^{1}H NMR spectrum. Deacetylation of the mixture **9** with sodium methoxide in methanol afforded separable **10** and **11** in 10:1 ratio in 88% overall yield.

Installation of an isopropylidene ketal[120] at O-5 and O-6, followed by epoxidation with diisopropylazodicarboxylate (DIAD) and triphenylphosphine (PPh_3) afforded **1** in 81% yield with none of its stereoisomer isolated (Figure 2.3).

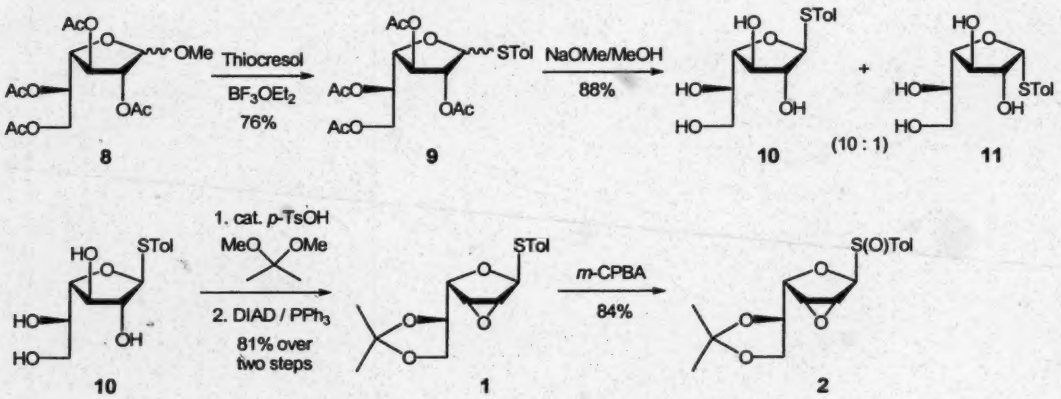


Figure 2.3. Syntheses of donor **1** and **2**.

Formation of the 2,3-epoxy group in **1** was clearly demonstrated by the marked upfield shift (~20 ppm) of signals for C-2 and C-3 in ^{13}C NMR spectrum, which appeared at 56.8 ppm and 54.9 ppm, respectively. However, it was impossible to determine the orientation of epoxide ring simply from the ^{1}H and ^{13}C NMR data. Fortunately, this compound was crystalline and a single-crystal X-ray diffraction study unambiguously showed that the epoxide moiety is *trans* to the tolyl moiety at C-1 and *cis* to the dioxolane group appended to the ring at C-4 (Figure 2.4).[121]

Thioglycoside **1** was readily oxidized into sulfoxide donor **2** upon treatment with *m*-chloro-perbenzoic acid (*m*-CPBA)[122] in dichloromethane in 84% yield.

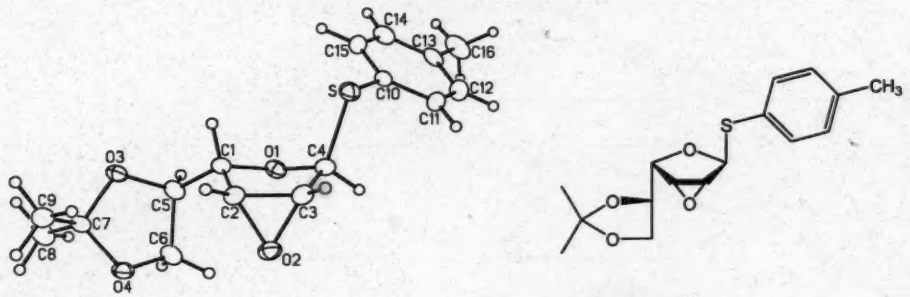


Figure 2.4. X-ray crystal structure of donor **1**.

2.2.2 Synthesis of 5,6-di-*O*-Benzyl and 5,6-di-*O*-Benzoyl Donors

With donor **1** in hand, we assumed that both benzyl and benzoyl protected donors could be prepared directly via acidic removal of the isopropylidene group and subsequent installation of benzyl or benzoyl protecting groups. However, attempts to remove the 5,6-*O*-isopropylidene protecting group failed, regardless of different acidic conditions

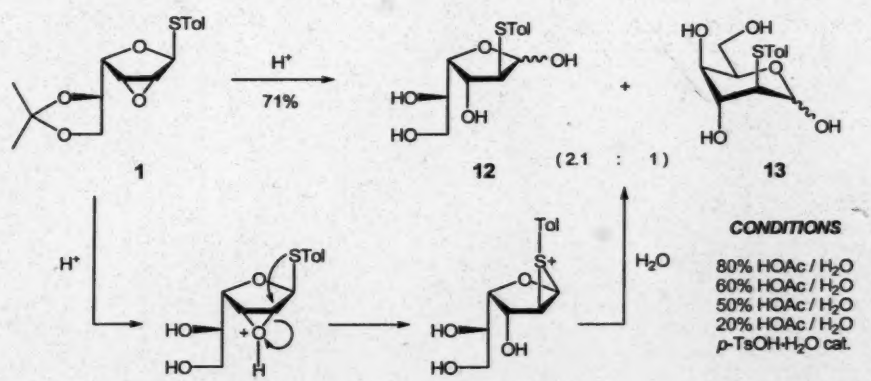


Figure 2.5. Failures in the removal of the isopropylidene group on donor **1**.

tried. TLC monitoring of reactions showed the formation of one major spot, different from starting material, which was isolated and proved to be a four-compound mixture, resulting from the migration of the thiocresol group upon acid-mediated opening of the epoxide moiety. A postulated mechanism for this migration is shown in Figure 2.5.

Our new efforts to prepare donor **3** and **5** involved a more labile orthoester installed at the O-5 and O-6 position instead of an isopropylidene ketal. This group was added upon reaction with trimethyl orthoacetate and *p*-TsOH. After epoxide formation under Mitsunobu conditions,[104] the resulting intermediate was subsequently washed with 0.3% aq. HCl solution to cleave the orthoester protecting group, while leaving the epoxide moiety intact. A mixture of O-5 and O-6 acetates was produced. Further treatment of the mixture under Zemplén conditions removed these acetyl groups to give compound **14** in 72% yield over four steps (Figure 2.6).

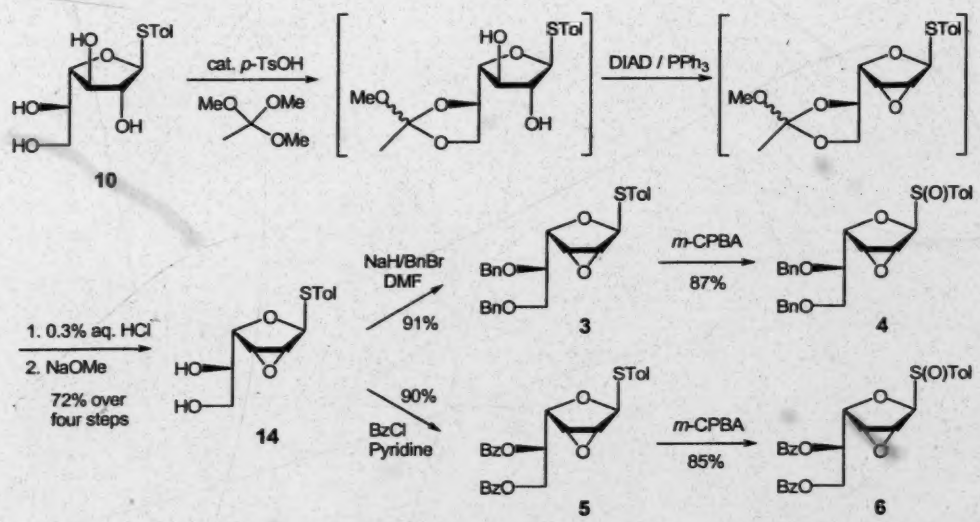


Figure 2.6. Syntheses of donors **3**, **4**, **5**, and **6**.

Subsequently, the benzylation and benzoylation reactions were carried out to give the desired donors **3** and **5** in excellent yields. The corresponding sulfoxide donors **4** and **6** were obtained after partial oxidation of the sulfur with *m*-CPBA in dichloromethane.

2.3 Distinguishing Anomeric Stereochemistry in 2,3-Anhydro-D-Gulofuranosides

Before investigating the glycosylation reactions with donors **1-6**, it was essential to establish a reliable criterion to easily distinguish the α- and β- 2,3-anhydro-D-gulo-furanosides, so that we could evaluate the outcome of the methodology. Previous work[123] in our laboratory indicated that the one-bond coupling constant between C-1 and H-1 in 2,3-anhydro-*O*-furanosides is diagnostic of the stereochemistry at the anomeric center and can be used for assigning the stereochemistry in 2,3-anhydro-*O*-glycosides. For 2,3-anhydro-*O*-glycosides, in which H-1 is *trans* to the epoxide moiety, $^{1}J_{C\text{-}1,\ H\text{-}1}$ = 163-168 Hz; while this hydrogen is *cis* to the oxirane ring, $^{1}J_{C\text{-}1,\ H\text{-}1}$ = 171-174 Hz.[123]

Because the panel of compounds studied in the previous work was based on glycosides with the α-*lyxo* and β-*ribo* configuration, model studies were necessary to verify the suitability of this parameter for differentiating 2,3-anhydro-D-gulofuranosides.

2.3.1 Synthesis of 2,3-Anhydro-β-D-gulofuranoside Models

Glycosylation of donor **9** with either *n*-octanol or *n*-octyl 2,3-anhydro-α-D-lyxofuranoside[123] afforded β-glycosides **15** (40% + 40% α-anomer and acyl migration

product) or **16** (89%) as the major products. Deacetylation with sodium methoxide, followed by installation of isopropylidene at O-5 and O-6, and the epoxide functionality at C-2 and C-3 positions provided the desired 2,3-anhydro-β-D- gulofuranosides **19** and **20** in 49% and 74% yield (Figure 2.7).

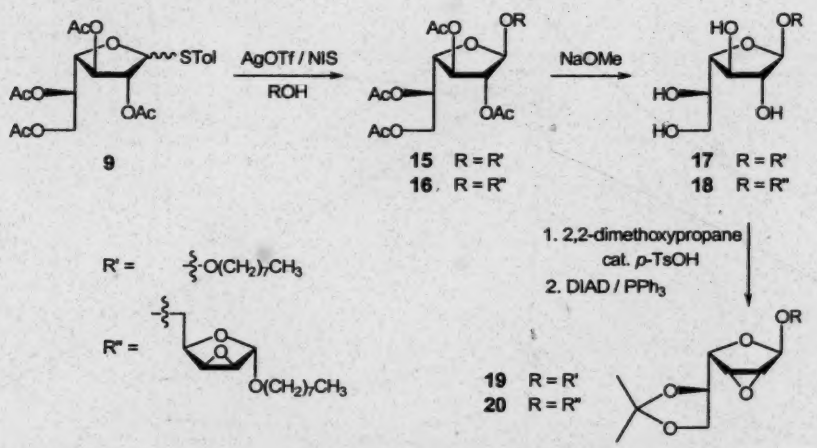


Figure 2.7. Syntheses of 2,3-anhydro-β-D-gulofuranoside models.

2.3.2 Synthesis of 2,3-Anhydro-α-D-gulofuranoside Models

To avoid neighboring group participation from C-2, the synthesis of the α-glycosidic linkage began with benzylated thioglycosides **21**, which were obtained from compound **9** after deacylation and then benzylation in excellent yield. Glycosylation of either *n*-octanol or octyl 2,3-anhydro-α-D-lyxofuranoside with **21** provided mixtures (79% and 70% respectively) of α and β glycosides. The anomeric mixtures were separated, and then subjected to catalytic hydrogenation to remove all benzyl groups. Glycosides **24** and **25** were subsequently treated under the same conditions as **17** and **18**

(Figure 2.7) to give the desired 2,3-anhydro-α-D-gulofuranosides **26** and **27** in 65% and 39% yield, respectively (Figure 2.8).

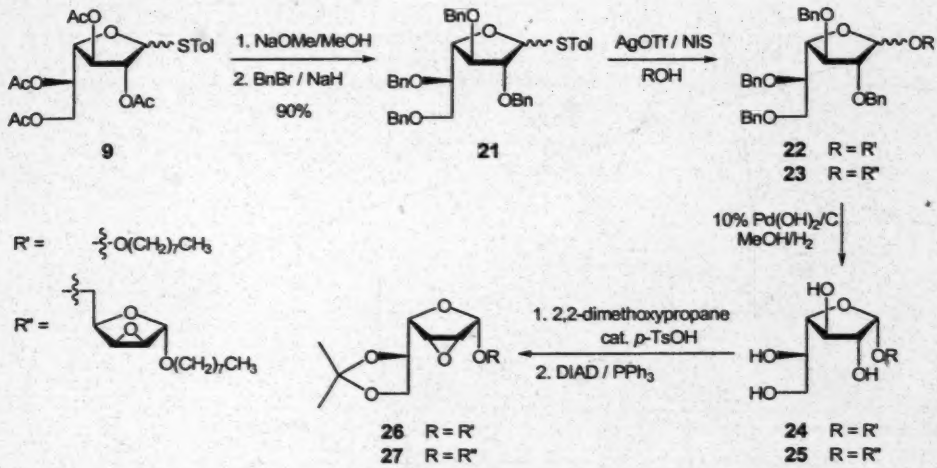


Figure 2.8. Syntheses of 2,3-anhydro-α-D-gulofuranoside models.

2.3.3 Data Analysis

NMR spectral data of compounds **19**, **20**, **26** and **27** were measured and analyzed, including H-1 chemical shifts, C-1 chemical shifts, and the coupling constants between C-1 and H-1 (Table 2.1). Neither the H-1 nor C-1 chemical shifts gave any clues as to anomeric stereochemistry. However, the results verified that the coupling constant $^1J_{C\text{-}1,\ H\text{-}1}$ is applicable to determine unequivocally the stereochemistry at the anomeric centre in 2,3-anhydro-D-gulofuranosides.

To summarize, when H-1 is *trans* to the epoxide moiety in 2,3-anhydro-α-D-gulofuranosides, $^1J_{C\text{-}1,\ H\text{-}1}$ = 163-167 Hz; when H-1 is *cis* to the oxirane ring in 2,3-anhydro-β-D-gulofuranosides, $^1J_{C\text{-}1,\ H\text{-}1}$ = 174 Hz.

	19	26	20	27
anomeric stereochemistry	β (H_1-O_{ep} *cis*)	α (H_1-O_{ep} *trans*)	β (H_1-O_{ep} *cis*)	α (H_1-O_{ep} *trans*)
H-1 (ppm)	5.09	5.08	5.16	5.18
C-1 (ppm)	101.3	101.6	101.8	101.6
$^1J_{C\text{-}1,\,H\text{-}1}$ (Hz)	174	163	174	167

Table 2.1. $^1J_{C\text{-}1,\,H\text{-}1}$ in 2,3-anhydro-D-gulofuranoside models.

2.4 Exploration of Stereoselectivity of Donors in Glycosylation Reactions

Success in the syntheses of desired donors **1-6** encouraged us to further examine the directing effect of the epoxide ring in the glycosidic bond formation.

2.4.1 Acceptors Examined in Glycosylation Reactions

To fully explore the stereoselectivity of donors **1-6** in glycosylation reactions, typical acceptors were selected, including primary, secondary, tertiary alcohols, and primary, secondary sugar acceptors (Figure 2.9).

2.4.2 Glycosylation Reactions and Data Analysis

The use of thioglycoside donors **1**, **3** and **5** in the glycosylation reactions was initially investigated. In these reactions, the thioglycoside was activated by the use of 1.2 equivalents of *N*-iodosuccinimide (NIS) and 0.3 equivalents of silver triflate (AgOTf) at -40 °C in dichloromethane. After stirring for 20 minutes, the reaction mixture was

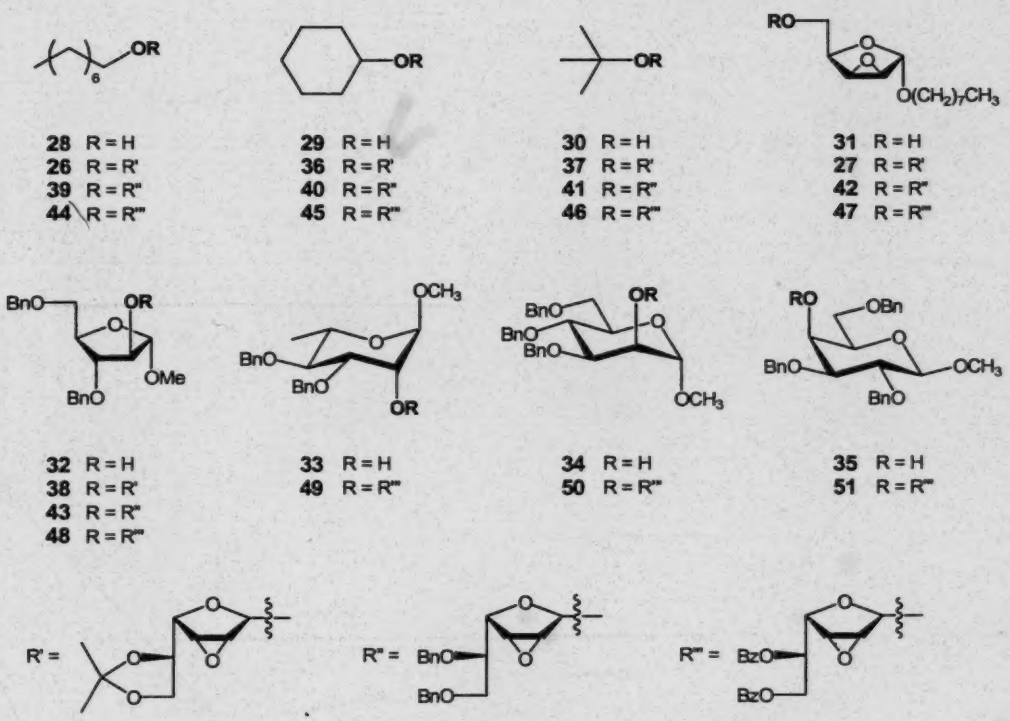


Figure 2.9. List of acceptors and glycosylation products.

warmed to -25 °C and kept until completion of the reaction. With sulfoxide donors **2**, **4** and **6**, we employed triflic anhydride (Tf_2O) activation in dichloromethane using the protocol developed by Crich[124, 125] and modified by our group.[104] Under these conditions, the sulfoxide was treated first with 1.2 equivalents of triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) and stirred at -78 °C for 10 minutes. The solution was then warmed to -40 °C and stirred for another 20 minutes prior to the addition of the alcohol. In addition, we also explored the BSP/Tf_2O method developed by Crich and co-workers[55] for the activation of thioglycoside **5** in order to compare the results with those obtained with the NIS/AgOTf method.

Entry	Donor	Activators	Acceptor	Product	$^1J_{C\text{-}1,H\text{-}1}$ (Hz)	% Yield	α : β ratio
1	**1** (STol)	NIS/AgOTf	**28**	**26**	163	82	α only
2	**1** (STol)	NIS/AgOTf	**29**	**36**	163	83	α only
3	**1** (STol)	NIS/AgOTf	**30**	**37**	160	82	α only
4	**1** (STol)	NIS/AgOTf	**31**	**27**	167	66[a]	α only
5	**1** (STol)	NIS/AgOTf	**32**	**38**	166	51[b]	α only
6	**3** (STol)	NIS/AgOTf	**28**	**39**	164	87	9:1
7	**3** (STol)	NIS/AgOTf	**29**	**40**	163	80	5:1
8	**3** (STol)	NIS/AgOTf	**30**	**41**	161	80	3:1
9	**3** (STol)	NIS/AgOTf	**31**	**42**	166	81	7:1
10	**3** (STol)	NIS/AgOTf	**32**	**43**	165	75	3:1
11	**5** (STol)	NIS/AgOTf	**28**	**44**	165	81	α only
12	**5** (STol)	NIS/AgOTf	**29**	**45**	164	79	α only
13	**5** (STol)	NIS/AgOTf	**30**	**46**	162	80	9:1
14	**5** (STol)	NIS/AgOTf	**31**	**47**	166	82	10:1
15	**5** (STol)	NIS/AgOTf	**32**	**48**	166	75	α only
16	**5** (STol)	NIS/AgOTf	**33**	**49**	168	78	8:1
17	**5** (STol)	NIS/AgOTf	**34**	**51**	168	72	8:1
18	**5** (STol)	BSP/Tf_2O	**31**	**47**	166	78	6:1
19	**5** (STol)	BSP/Tf_2O	**32**	**48**	166	74	7:1

[a] 28% migration product was isolated (see text) [b] 24% migration product was isolated (see text)

Table 2.2. Glycosylation of 2,3-anhydro-D-gulofuranosyl thioglycosides with various acceptors.

Entry	Donor	Activators	Acceptor	Product	$^1J_{C\text{-}1,H\text{-}1}$ (Hz)	% Yield	α : β ratio
1	**2** S(O)Tol	Tf_2O	**28**	**26**	163	78	α only
2	**2** S(O)Tol	Tf_2O	**29**	**35**	163	79	α only
3	**2** S(O)Tol	Tf_2O	**30**	**36**	160	71	4:1
4	**2** S(O)Tol	Tf_2O	**31**	**27**	167	71	6:1
5	**2** S(O)Tol	Tf_2O	**32**	**38**	166	73	5:1
6	**4** S(O)Tol	Tf_2O	**28**	**39**	164	82	α only
7	**4** S(O)Tol	Tf_2O	**29**	**40**	163	81	α only
8	**4** S(O)Tol	Tf_2O	**30**	**41**	161	76	10:1
9	**4** S(O)Tol	Tf_2O	**31**	**42**	166	79	α only
10	**4** S(O)Tol	Tf_2O	**32**	**43**	165	72	α only
11	**6** S(O)Tol	Tf_2O	**28**	**44**	165	87	α only
12	**6** S(O)Tol	Tf_2O	**29**	**45**	164	81	α only
13	**6** S(O)Tol	Tf_2O	**30**	**46**	162	78	α only
14	**6** S(O)Tol	Tf_2O	**31**	**47**	166	82	α only
15	**6** S(O)Tol	Tf_2O	**32**	**48**	166	76	α only
16	**6** S(O)Tol	Tf_2O	**34**	**50**	168	75	14:1
17	**6** S(O)Tol	Tf_2O	**35**	**51**	168	72	α only

Table 2.3. Glycosylation of 2,3-anhydro-D-gulofuranosyl sulfoxides with various acceptors.

The results presented in Tables 2.2 and 2.3 clearly indicate that donors **1-6** do efficiently glycosylate a range of alcohols with a high degree of stereocontrol. Primary, secondary, and tertiary alcohols are readily glycosylated in high yields. Primary and secondary carbohydrate acceptors work well also. In all examples, the major or exclusive

product is the α-glycoside, in which the newly formed glycosidic linkage is *cis* to the epoxide moiety, and *trans* to the anomeric hydrogen.

Based on the yields and α:β ratios, some trends can be identified. First, in general, the yields and α-selectivity of the glycosylation reactions decreases with increasing steric hindrance on the acceptor. Tertiary alcohols (Table 2.2 Entry 8 and Table 2.3 Entry 3) and carbohydrate secondary alcohol acceptors (Table 2.2 Entry 10 and Table 2.3 Entry 5) normally give lower yields and poorer selectivities compared to other acceptors. However, the α:β ratios are better than 4:1 in most cases. The worst selectivity (3:1, α:β) is observed in the reactions of relatively hindered alcohols **30** and **32** with thioglycoside **3** (Table 2.2 Entries 8 and 10).

Second, a comparison of the glycosylation reactions involving sulfoxides **2**, **4** and **6** (Table 2.3) with thioglycoside **1**, **3** and **5** (Table 2.2) reveals that these sulfoxide donors generally provide better α-selectivities, regardless of the structure of the acceptor. In addition, different activation methods for thioglycoside **5** do not affect the stereoselectivity of the glycosylation reactions. The BSP/Tf_2O method works well too; However reactions are slower.

Third, the use of different protecting groups at C-5 and C-6 positions influence the reaction outcome. Glycosylation with both benzyl- and benzoyl- protected donors **3-6** give somewhat higher yields and better α-selectivities than isopropylidene protected donors **1** and **2**, especially when the carbohydrate acceptors are involved in the reactions (Table 2.3 Entries 4, 5 and Table 2.3 Entries 4, 5). With thioglycoside **1**, we observed that

significant amounts of 2-deoxy-2-thiocresyl-α-D-idofuranosides (Figure 2.10) were produced in addition to the desired 2,3-anhydro-D-gulofuranosyl glycosides (Table 2.2 Entries 4 and 5). These side reactions are attributed to the trace amount of triflic acid generated as the reaction proceeds, which induces the rearrangement process presumably via a pathway similar to that shown in Figure 2.5.

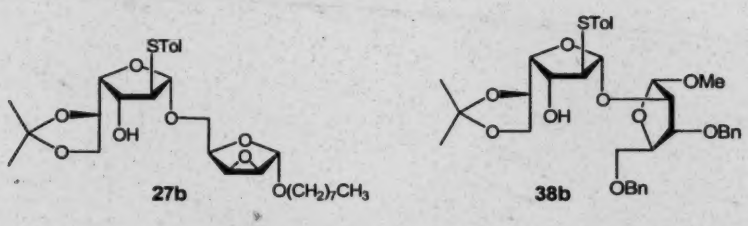


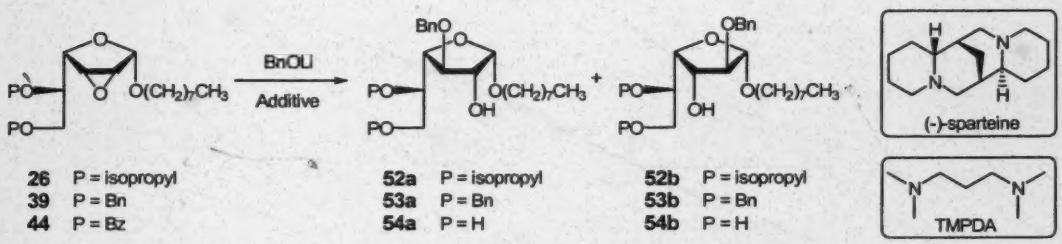
Figure 2.10. Thiocresol migration products isolated in glycosylation reactions.

2.5 Exploration of Epoxide Opening Reactions

Because the glycosylation via 2,3-anhydro donors **1-6** has been proven to be a efficient pathway for the syntheses of 2,3-anhydro-α-D-gulofuranosides, it is critical that methods be developed for the regioselective opening of the oxirane ring in the glycoside products.

Our experience on the syntheses of α- and β-D-arabinofuranosides[104] indicated that the combined use of lithium benzylate (BnOLi) and (-)-sparteine in benzyl alcohol at 70 °C afforded the best regioselectivity and high yields for the epoxide opening reactions. Therefore, similar reaction conditions were believed to be a suitable pathway to open these 2,3-anhydro-α-D-gulofuranosides as well. We carried out the reaction of compounds

26, **39** and **44** at 75 °C with 6.0 equivalents of BnOLi in benzyl alcohol, either in presence or absence of 1.2 equivalent of the additive, to compare the effects of (-)-sparteine on these reactions. In addition to (-)-sparteine, *N,N,N',N'*-tetramethyl-1,3-propanediamine (TMPDA) was also studied as an additive. The reaction time varied from 6 to 12 hours (Figure 2.11).



26 P = isopropyl
39 P = Bn
44 P = Bz

52a P = isopropyl
53a P = Bn
54a P = H

52b P = isopropyl
53b P = Bn
54b P = H

Figure 2.11. Epoxide ring opening reactions with BnOLi.

Solely on the basis of steric hindrance considerations, nucleophilic attack at either C-2 or C-3 would be expected to be equally likely, as the top face of the furanose ring in the 2,3-anhydro-D-gulofuranoside has no substituents to bias the approach of the nucleophile to the epoxide. However, previous work[104] demonstrated that, although the possibility of attacking C-2 and C-3 is similar, nucleophilic attack at C-3 would be preferred, but not exclusively. Attack of nucleophile at C-2 affords a product with the D-idofuranose (Ido*f*) stereochemistry, whereas attack at C-3 provides a product with the D-galactofuranose (Gal*f*) stereochemistry.

The yield and Gal*f*:Ido*f* ratio data presented in Table 2.4 reveal that most reactions give acceptable conversion yields, ranging from 75% to 85%; however the

regioselectivities of these reactions are not very high. The observed regiocontrol in these reactions is likely attributed mostly to the steric effect of the protecting groups at C-5 and C-6 positions. Substrates possessing protecting benzyl groups give the worst selectivity, presumably because the bulky aromatic ring at C-5 prohibits the nucleophilic attack at C-3, no matter if the additive (-)-sparteine is added or not (Entries 3 and 4). The presence of an isopropylidene ketal also exerts a steric effect on the regioselectivity, only less due to its smaller size. Nevertheless, marked increases and a reversal in regioselectivity were observed when the benzoyl protected substrate **44** was used (Entries 5 and 6). In these processes, the base-labile benzoyl groups are likely immediately removed upon the addition of the alkoxide, followed by the nucleophilic attack at C-3 to open the epoxide ring. In these cases, the alkoxide groups at C-5 and C-6 of the intermediate might facilitate C-3 attack, due to their smaller size or via a somehow unknown mechanism.

Entry	Substrate	Additive	Products (Gal*f*, Ido*f*)	Conversion %	Ratio (Gal*f*: Ido*f*)
1	**26**	—	**52a , 52b**	75	1 : 1.8
2	**26**	(-)-sparteine	**52a , 52b**	75	1 : 1.5
3	**39**	—	**53a , 53b**	84	1 : 3.2
4	**39**	(-)-sparteine	**53a , 53b**	85	1 : 2.9
5	**44**	—	**54a , 54b**	76	3.3 : 1
6	**44**	(-)-sparteine	**54a , 54b**	78	4.8 : 1
7	**44**	TMPDA	**54a , 54b**	82	1.8 : 1

Table 2.4. Examination of nucleophilic epoxide opening with BnOLi.

Furthermore, the addition of (-)-sparteine seems to play a positive role in the regioselectivity. Although there is no dramatic increase in the reaction speed observed as in synthesis of β-D-arabinofuranosides, the improvement in reaction selectivity could support previous results and encourage further investigation into the mechanism of these reactions. Because the optimization and mechanistic study of these epoxide opening reactions are being carried out by other members in our group, I did not study this further.

2.6 NMR Investigation into the Mechanism of Glycosylations with Sulfoxide Donors

As described earlier, the predominant, or frequently only, products of glycosylation reactions between an alcohol and a 2,3-anhydrosugar donor, are the ones in which the newly formed glycosidic bond is *cis* to the epoxide moiety. The extremely high stereocontrol observed was intriguing and we became interested in understanding the origin of this stereoselectivity. Experiments were therefore carried out to probe the mechanism of the glycosylations with the glycosyl sulfoxide donors.

2.6.1 Proposed Mechanistic Pathway for Glycosylation with Sulfoxides

The activation protocol used for glycosylation with sulfoxide donors involved first treatment of the sulfoxide with 1.2 equivalents of triflic anhydride (Tf_2O) in the presence of 4.0 equivalents of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at -78 °C in dry CH_2Cl_2. After stirring for 10 minutes, the mixture was warmed to -40 °C and stirred for

20 minutes before the addition of the alcohol. Based on our observation and earlier work by Crich and coworkers[125] on the mechanism of the stereoselective β-D-mannopynoside synthesis and Lowary and coworkers[105] on the synthesis of β-D-arabinofuranosides, we proposed that, a triflate intermediate forms before the addition of alcohol, which in turn, leads to the high stereoselectivity (Figure 2.12).

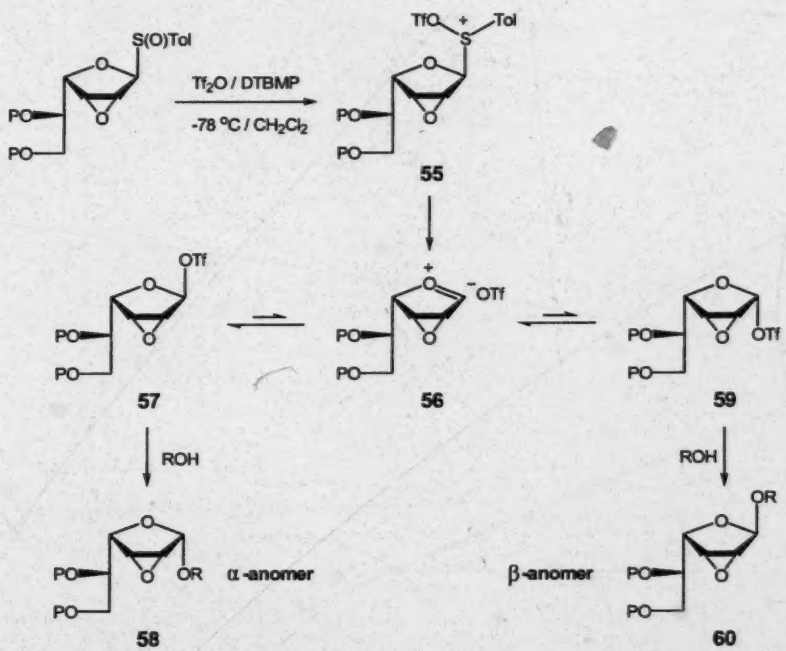


Figure 2.12. Proposed mechanistic pathway of glycosylations with sulfoxide donors.

In the first step, Tf_2O is added to the sulfoxide in the presence of DTBMP, leading to the formation of an ion-pair **56** by way of the activated sulfoxide derivative **55**. In the absence of any other nucleophiles, **56** would be in equilibrium with glycosyl triflates **57** and **59** at low temperature. It is expected that β-triflate **57** would be the most stable species in this equilibrium and would be predominant after some time. In the second step,

with the addition of acceptor into the reaction mixture, a S_N2 like displacement would occur with the triflate **57** as a leaving group, leading to the formation of α-glycoside **58**.

The stereocontrol of this process would be therefore be determined by the relative concentrations of **56, 57**, and **59**. The latter two species would lead to a highly stereo-selective reaction, via S_N2 displacement of the triflate by the alcohol. On the contrary, ion-pair **56** would directly undergo the coupling process by non-stereoselective pathway, leading to the formation of a mixture of glycosides. It is reasonable to explain the selectivity observed in the glycosylation results via a pathway involving intermediate **57**.

2.6.2 Detection of a Triflate Intermediate by Low-Temp. NMR Spectroscopy

Although the proposed mechanism is plausible, it is essential to establish an experimental method to verify the existence of the postulated triflate intermediate. On the basis of other mechanistic studies,[105, 125] we planned to detect the presence of triflate intermediate via low-temperature NMR spectroscopy, using sulfoxide donor **4**. The triflate species **62** can be differentiated from the sulfoxide **4** straightforwardly by ^1H NMR and ^{13}C NMR spectroscopy. Moreover, distinguishing the ion-pair species **61** and

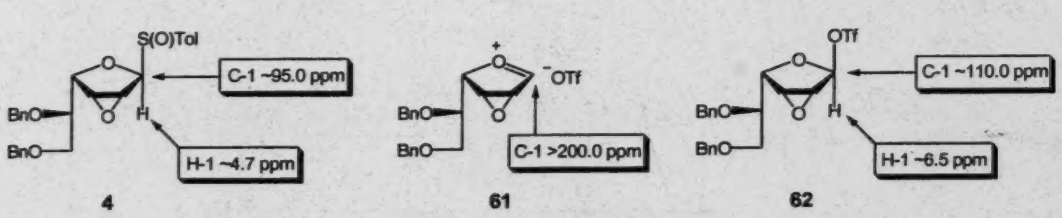


Figure 2.13. Expected differences of intermediates by NMR spectroscopy.

triflate intermediate **62** can be achieved by ^{13}C NMR spectroscopy, in that the chemical shift of C-1 in the oxonium ion should be above 200 ppm[126] (Figure 2.13).

We first obtained the ^{1}H NMR and ^{13}C NMR spectral data from the mixture of sulfoxide donor **4** and DTBMP in CD_2Cl_2 at -78 °C, which was labeled as 0 minute of the reaction. The partial spectrum, in the region between 3.4 ppm and 6.6 ppm, is shown in Figure 2.14 (a). The sample tube was then removed from NMR spectrometer and kept at -78 °C in a cooling bath. Tf_2O was added carefully and quickly to the mixture, and the tube was immediately placed in the cooled spectrometer. After a standard shimming process, the first ^{1}H NMR spectrum was recorded two minutes after addition of Tf_2O.

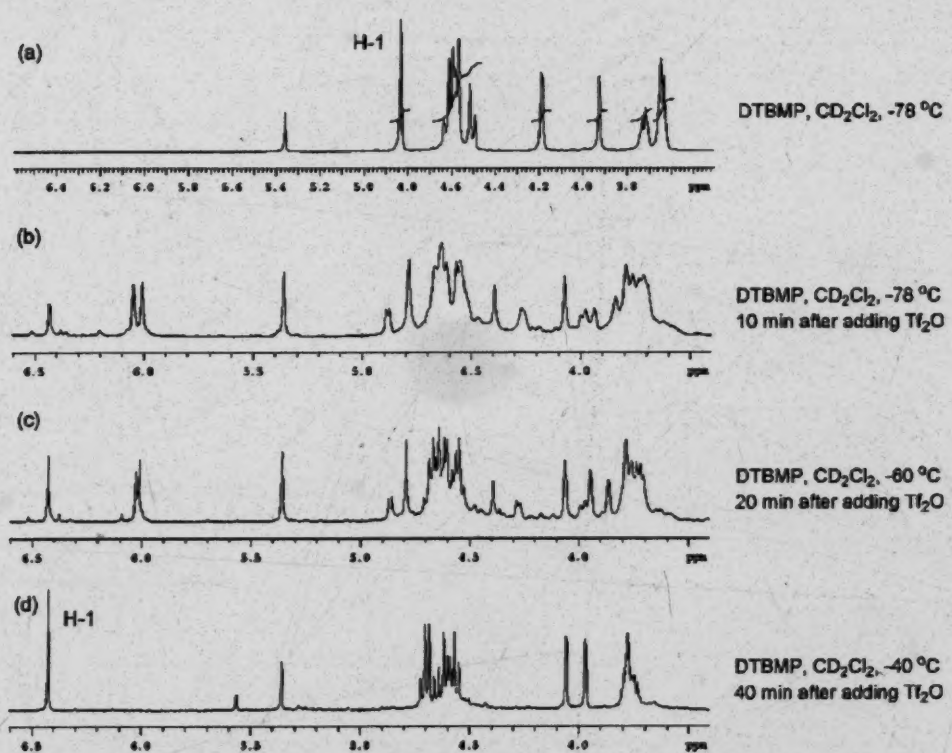


Figure 2.14. Detection of triflate intermediate **62** by ^{1}H NMR spectroscopy.

The reaction was tracked in every five minutes, and some characteristic spectra are shown in Figure 2.14.

The mechanism of the reaction can be probed upon analysis of the ^{1}H NMR spectral data we recorded. Activation of the sulfoxide functionality was initiated with the addition of Tf_2O, and after 10 minutes, three newly formed peaks were observed in the region between 6.0 ppm and 6.5 ppm. This event was also accompanied with the weakening of the intensity of the anomeric hydrogen signal (H-1). A further increase in the intensity of the signal at ~6.4 ppm was obtained at 20 minutes after activation when the temperature of the NMR spectrometer was warmed to -60 °C. It was also noticeable that the pattern of two signals at ~6.0 ppm changed and became closer with each other, which correspond to the other reaction intermediates of unknown structure. After raising the reaction temperature to -40 °C, the mixture at 40 minntes after the activation gave a clean spectrum with only one intermediate visible, bearing an anomeric hydrogen at ~6.4 ppm. The chemical shift of this anomeric hydrogen is consistent with it being a glycosyl triflate.[125] Furthermore, the other two peaks at ~6.0 ppm completely disappeared at this stage. Although the appearance of peaks at ~6.0 ppm indicated that the reaction process might have undergone a more complicated pathway or formed other intermediates than we proposed, data collected at 40 minutes after activation correspond to what we expected, and fully support our earlier hypothesis.

^{13}C NMR spectral data were recorded as well, and the region between 50 ppm and 112 ppm is shown in Figure 2.15. Comparison of the spectrum at 0 minute (sulfoxide **4**)

and the spectrum after 40 minutes at -40 °C (reaction intermediate) revealed a huge difference between two anomeric carbon signals. A shift of the anomeric carbon from 94.7 ppm to 109.8 ppm proved the formation of triflate intermediate **62**, instead of the ion-pair species **61**.

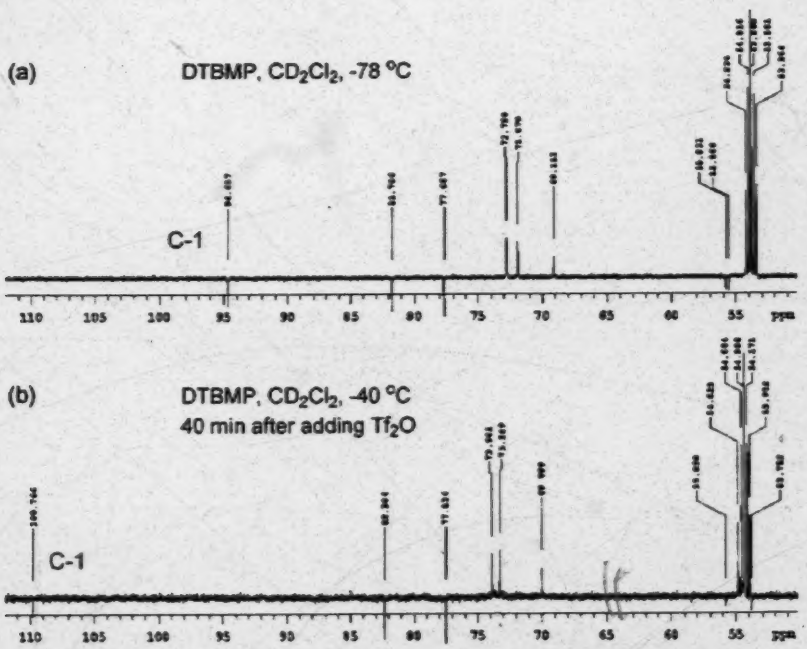


Figure 2.15. Detection of triflate intermediate **62** by ^{13}C NMR spectroscopy.

2.6.3 Attempt to Synthesize Authentic Triflate Intermediate 62

Although the detection of the triflate intermediate was successful, through the demonstration of single compound in the NMR spectra, the stereochemistry of this intermediate was not fully confirmed yet. Our assumption that the intermediate was **62** is based on the glycosylation results and a proposed S_N2-like reaction in the last step. We therefore attempted to verify the stereochemistry of triflate intermediate.

In our previous investigation, the coupling constant $^{1}J_{C\text{-}1,\ H\text{-}1}$ was useful in the identification of the relative direction between newly formed glycosidic bond and epoxide moiety. However, this factor failed in this anomeric triflate case, because carbohydrate derivatives with a strong electron withdrawing group at anomeric center have larger $^{1}J_{C\text{-}1,\ H\text{-}1}$ magnitude than *O*-glycosides. The synthesis of an authentic sample of **62** was therefore attempted to verify the stereochemistry of the triflate intermediate.

Hydrolysis of donor **3** was accomplished by the activation of NIS and AgOTf in the presence of H_2O to provide **63**, in which the β-stereochemistry of anomeric center was conformed by $^{1}J_{C\text{-}1,\ H\text{-}1}$ = 174 Hz. The synthesis and detection of authentic triflate **62** was subsequently carried out in the NMR tube at -78 °C. Unfortunately, the reaction slowly proceeded and did not complete even after the temperature was gradually raised to room temperature. Nor was any trace amount of triflate detected during the process. Instead, four other anomeric signals besides that for compound **63** were observed, which were verified to be 1→1 linkage dimers by ESI-MS spectroscopy. We propose that, as soon as the triflate intermediate is formed, it couples with the unreacted **63** to generate dimers, and hence the triflate **62** has too short a life time to be detected (Figure 2.16).

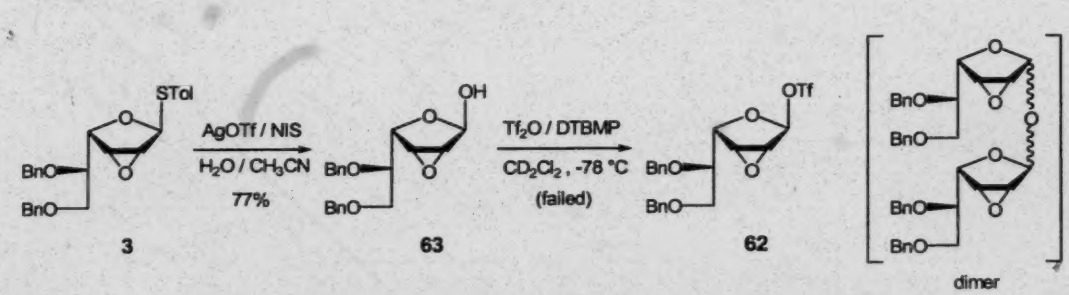


Figure 2.16. Attempt to synthesize authentic sample of **62**.

2.7 Conclusion

In summary, we are able to demonstrate that 2,3-anhydro-D-gulofuranosyl thioglycosides and glycosyl sulfoxides **1-6** can be used in highly stereoselective synthesis of α-D-galactofuranosides. The major products of the glycosylation reactions are those in which the newly formed glycosidic bond is *cis* to the epoxide moiety. These species represent a fundamentally new class of glycosylating agent in which the hydroxyl groups at C-2 and C-3 are "protected" as an epoxide.

We have also demonstrated the regioselective opening of the oxirane moiety to provide products with the α-D-galactofuranose stereochemistry. However, the reaction condition has not been optimized yet. The main advantage of this discovery is that, when the epoxide moiety in 2,3-anhydro-α-D-gulofuranosides is opened by lithium benzylate, the free hydroxyl group at C-2 can potentially be used as acceptors for the synthesis of oligosaccharides possessing 1→2 glycosidic linkage.

Overall, the best results were observed when benzoylated 2,3-anhydrosugar donors were used in glycosylation reactions, and the corresponding benzoylated substrates also gave the best results in the epoxide opening reactions. Benzoylated thioglycoside **5** and sulfoxide donor **6** are the best glycosylating agents in the synthesis of α-D-galactofuranosides. Applications of this methodology will be discussed further in Chapter 3.

CHAPTER 3

SYNTHESIS OF α-D-GALACTOFURANOSIDES VIA 2,3-ANHYDROSUGARS. APPLICATION OF METHODOLOGY TO TARGETS

3.1 Introduction

The investigations described in Chapter 2 clearly demonstrate the potential of 2,3-anhydro-D-gulofuranose derivatives in the synthesis of oligosaccharide motifs containing α-D-galactofuranosyl residues, which are fragments of bacterial or fungal cell wall polysaccharides. We therefore employed this method to synthesize a number of oligosaccharide targets, including a disaccharide motif **64** present in the bacterial lipopolysaccharide[112] produced by *Salmonella typhimurium 902*, the disaccharide

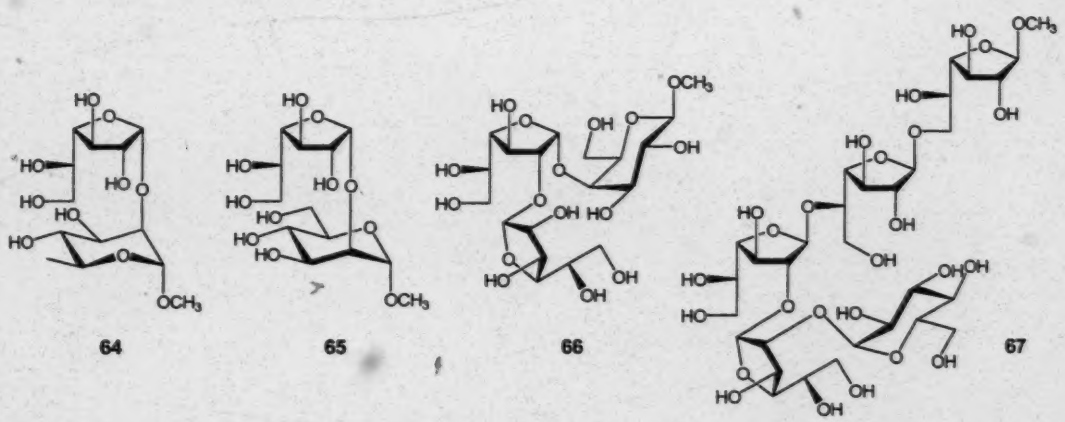


Figure 3.1. Target oligosaccharides containing α-D-galactofuranosyl residues.

repeating unit **65** of *Talaromyces flavus 310* cell wall polysaccharide,[107] the trisaccharide motif **66** structurally similar to the repeating unit of antigenic polysaccharide[101] generated by *Eubacterium saburreum T19*, and the pentasaccharide repeating unit **67** of *Penicillium varians* cell-wall polysaccharides (Figure 3.1).[113]

3.2 Synthesis of a Disaccharide Motif Present in Bacterial Lipopolysaccharide Produced by *Salmonella typhimurium 902*

The potential of our methodology can be demonstrated by the successful synthesis of a disaccharide unit of the lipopolysaccharide[112] from the *Salmonella Typhimurium 902* strain. The preparation of known monosaccharide acceptor **33**[127] is briefly outlined in Figure 3.2. Starting from commercially available L-rhamnose, compound **69** was prepared by the installation of an isopropylidene moiety on O-2 and O-3 and a benzyl group on O-4. Removal of the isopropylidene group was then carried out with a catalytic

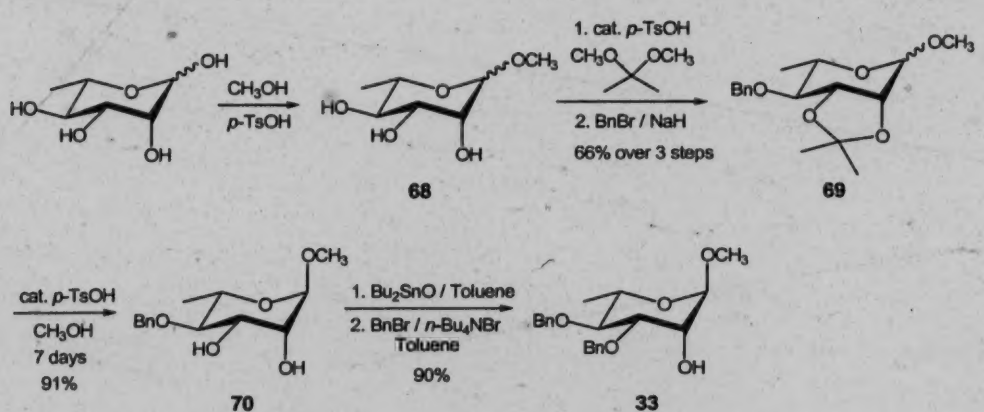


Figure 3.2. Synthesis of acceptor **33**.

amount of *p*-toluenesulfonic acid in methanol. Under these conditions, the reaction product fully equilibrated to the pure α-anomer **70**, which was isolated in 91% yield. Regioselective protection of the equatorial hydroxyl group at C-3 via the stannylidene acetal afforded the desired acceptor **33** in excellent yield.

The glycosylation reaction of donor **5** with acceptor **33** promoted by silver triflate and NIS at -40 °C gave disaccharide **49** in 78% overall yield in a 7:1 α:β ratio (Figure 3.3). The desired α-anomer **49** was successfully separated from β-anomer, and the oxarine ring was subsequently opened by the addition of BnOLi in benzyl alcohol solution in the presence of (-)-sparteine at 75 °C to give the disaccharide derivative **71** in 78% overall yield. The regioselectivity of this reaction was 5:1 (Gal*f*:Ido*f*), which is acceptable considering that the reaction condition was not optimized yet. Hydrogenation of compound **71** with 10% palladium on charcoal in methanol successfully removed all

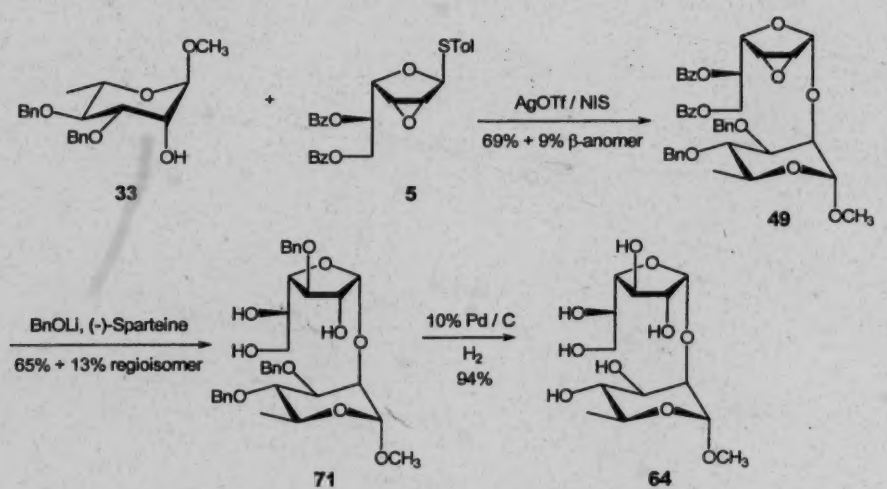


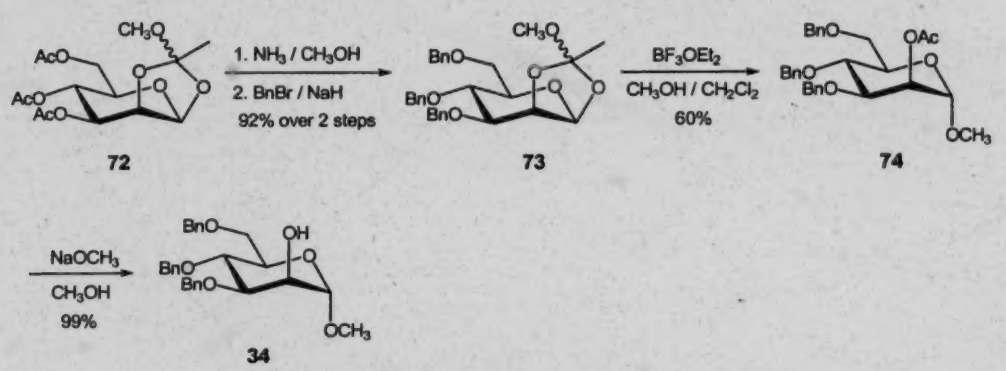
Figure 3.3. Synthesis of disaccharide **64**.

the benzyl protecting groups and afforded final disaccharide motif **64** of *S. typhimurium 902* in 94% yield.

3.3 Synthesis of the Disaccharide Repeating Unit of *Talaromyces flavus 310* Cell Wall Polysaccharide

In 1993, an α-Gal*f*-containing polysaccharide was identified[107] in the cell-wall polysaccharides from the *T. flavus 310* fungal strain, which is composed of disaccharide repeating units of α-D-Gal*f*-(1→2)-α-D-Man*p*. To further demonstrate the utility as our methodology, we synthesized the disaccharide motif **65**, employing 2,3-anhydrosugars in the key step to install the α-glycosidic linkage.

Preparation of known acceptor **34**[128] was achieved in four consecutive steps from a known intermediate **72** (Figure 3.4). We employed 7 *N* ammonia in methanol solution to remove all the acetyl groups from **72**, instead of the traditional Zemplén conditions.



72 **73** **74** **34**

Figure 3.4. Synthesis of acceptor **34**.

Benzylation was carried out directly on the deacylated crude product to generate **73** in excellent yield. The orthoester functionality in **73** was then opened in the presence of $BF_3 \cdot OEt_2$ to form methyl α-D-mannopyranoside **74,** which was readily converted to **34** by removal of the acetyl group on O-2.

With the acceptor **34** in hand, we first attempted the glycosylation of compound **34** with thioglycoside **5** (Figure 3.5). Unfortunately, this reaction gave only 50% overall yield of product in an anomeric ratio of 1:1.3 (α:β). Moreover, the thiocresol migrated product was also observed in a marked 20% yield.

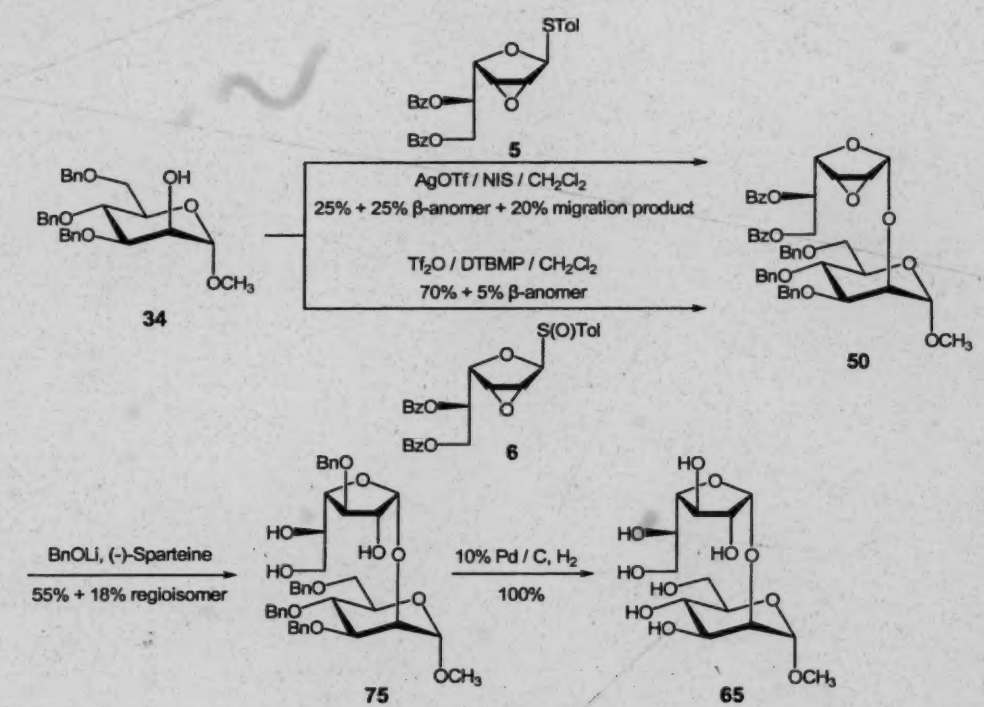


Figure 3.5. Synthesis of disaccharide **65**.

Due to the absence of stereoselectivity in the glycosylation reaction involving thioglycoside **5**, we attempted the reaction of sulfoxide donor **6** coupling with **34** instead.

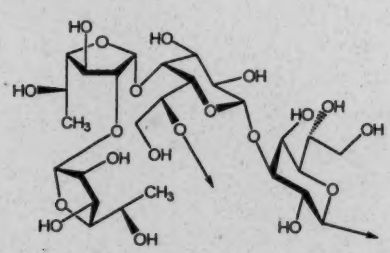
Following the reaction protocol for sulfoxide donors, disaccharide derivative **50** was successfully obtained in 70% yield in a 14:1 α:β ratio. The α-isomer was separated and then treated with BnOLi and the additive (-)-sparteine at 75 °C to open the oxarine ring. Catalytic hydrogenolysis of compound **75** to remove all the benzyl protecting groups gave the target disaccharide motif **65** in quantitative yield.

Interestingly, the glycosylation of thioglycoside donor **5** with sugar alcohol **34** was non-stereoselective, yielding almost equal amounts of both anomers. This was absolutely out of our expectation. Although the sulfoxide donor **6** successfully produced the desired α-glycoside, we still found about 5% β-anomer present. This is the only example for glycosylations of sulfoxide donor **6** in which the β-glycoside has been isolated. As discussed before, the stereoselectivity and the yield of this methodology are substrate-dependent. The properties of acceptors, such as reactivity, the position of free hydroxyl group, and even its conformation, can affect the glycosylation results.

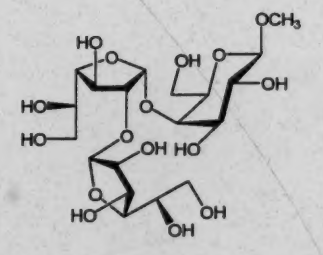
3.4 Synthesis of a Trisaccharide Related to a Motif Present in the Antigenic Polysaccharide Produced by *Eubacterium saburreum T19*

Eubacterium saburreum is an organism that has been detected in dental plaque. Its T19 strain settles in the human oral cavity and produces a cell-surface polysaccharide antigen of unique chemical composition.[101] In 2003, Ferrières and co-workers reported the first synthetic studies of the structure in which the D-fucofuranosyl residue was

introduced via intramolecular aglycon delivery.[100] The details of this synthesis have been described in Chapter 1 (Figure 1.25).



Eubacterium saburreum T19



66

Figure 3.6. Polysaccharide antigen generated by *E. saburreum T19* and the synthetic target **66**.

Considering that D-fucose is 6-deoxy-D-galactose, our methodology is expected to be suitable for the synthesis of fragments of this antigenic polysaccharide. Therefore, we chose to synthesize a trisaccharide **66**, in which the heptopyranoside residue was replaced by a galactopyranosyl residue and the D-fucofuranosyl moieties were replaced by D-galactofuranosides (Figure 3.6).

3.4.1 Synthesis of Disaccharide Intermediate 51 via 2,3-Anhydrosugar Donors

The synthesis of galactopyranoside **35**[129] needed for the reducing end of target trisaccharide **66** began with the installation of benzylidene acetal on O-4 and O-6 of commercially available methyl β-D-galactopyranoside. The other two hydroxyl groups were protected as benzyl ethers to yield compound **76** in 56% yield over two steps.

Regioselective opening of acetal by the combined use of sodium cyanoborohydride and triflic acid afforded 4-OH free intermediate **35** (Figure 3.7).

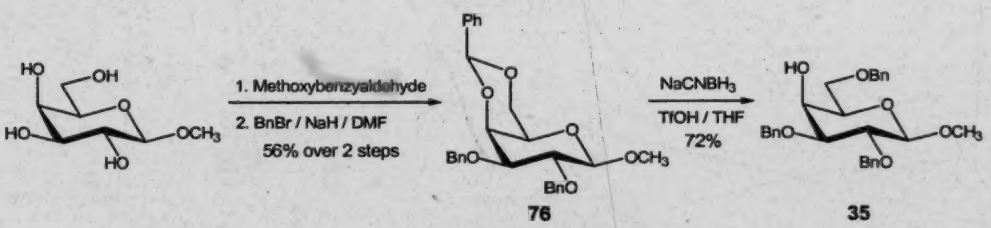


Figure 3.7. Synthesis of reducing end residue **35**.

The hydroxyl group at C-4 in galactopyranosides is usually the least reactive in glycosylation reactions, because of the combination effects of axial orientation and the bulkiness of adjacent protecting group on O-3 and O-6. However, it was worth trying to see how our methodology works. The glycosylation reaction of **5** and **35** was attempted first. Disaccharide **51** was prepared in an overall 70% yield with an α:β ratio of 8:1. We employed sulfoxide **6** as the glycosyl donor for this coupling reaction as well. A slight

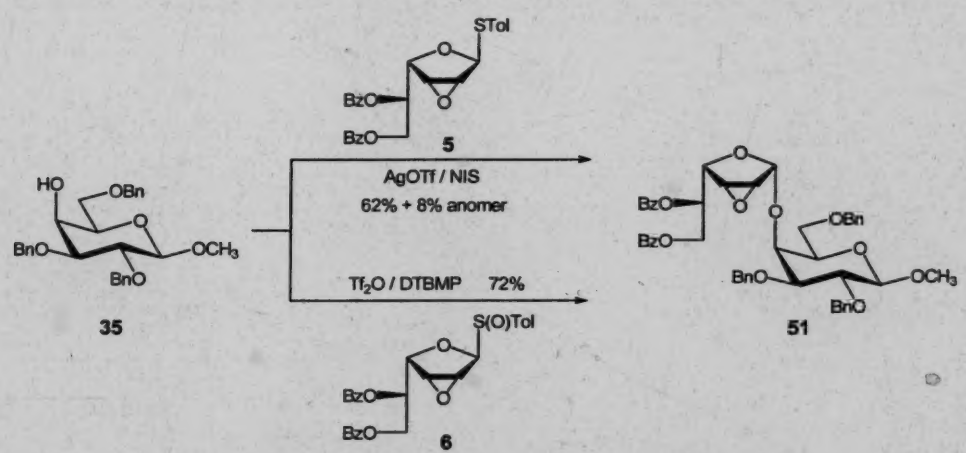


Figure 3.8. Synthesis of disaccharide intermediate **51**.

improvement was observed as only the α-anomer was obtained in 72% yield. The results are inspiring, considering the low inherent reactivity of acceptor **35** (Figure 3.8).

The next step involved the regioselective opening of epoxide functionality. In the presence of (-)-sparteine, nucleophilic attack of C-3 from the top face of furanosyl ring was preferred, and the epoxide in **51** was successfully opened to provide the desired intermediate **77** in 69% yield plus 5% of the regioisomer. The formation of product **77** was confirmed by the coupling constant $^{3}J_{\text{H-1, H-2}}$ = 5.1 Hz, which is typical for *cis* hydrogens in furanosides. The isopropylidene ketal was then installed to form dioxolane **78**, in which the 2-OH is free and ready for further glycosylation (Figure 3.9).

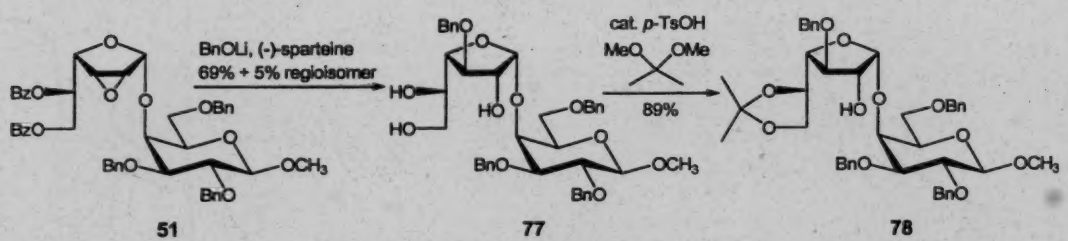


Figure 3.9. Synthesis of disaccharide acceptor **78**.

3.4.2 Synthesis of Trisaccharide 66 via 2,3-Anhydrosugar Donor

To install the α-(1→2) linkage in trisaccharide motif **66**, 2,3-anhydro glycosyl donor **5** or **6** was expected to be involved in the glycosylation coupling again. As usual, thioglycoside **5** was applied to the synthesis of **79** first. Following the protocol used, we investigated the glycosylation reaction of **5** with disaccharide acceptor **78**. The reaction seemed to work properly, based on the observation that the color of the reaction solution

changed to dark red. Nevertheless, TLC of the reaction showed three major compounds, which appeared more polar than the expected product. Isolation and identification of the mixture indicated that one of them was hydrolyzed donor, and the other two were unreacted acceptor **78** and a degraded trisaccharide, in which the isopropylidene ketal had been cleaved. However, a small amount of trisaccharide **79** could be isolated. The three anomeric protons could be clearly identified in the ^{1}H NMR spectrum. However, when the ^{13}C NMR spectrum was recorded in $CDCl_3$ over a longer time, we observed gradual decomposition of the compound. After isolation and analysis of this decomposed component, it was found that the ketal functionality was cleaved, resulting in decomposition. It was reasoned that, the acid-labile isopropylidene ketal was cleaved by the trace amount of acid in $CDCl_3$. During the glycosylation reaction process, a small amount of triflic acid was generated, which would also cleave the isopropylidene ketal, especially at extended reaction times. Because acceptor **78** possesses a hindered 2-OH, longer reaction times were required, which increased the possibility of the cleavage of isopropylidene ketal group. The enhanced susceptibility of the isopropylidene ketal in **79** to acid hydrolysis may result from the hindered nature of the central α-D-galactofuranosyl residue of the trisaccharide.

Reminded of the neutral conditions of sulfoxide glycosylation, we coupled sulfoxide **6** and acceptor **78**. After the addition of the acceptor, the reaction mixture was gradually warmed to room temperature and kept stirring for 24 hours to ensure completion of the reaction. Trisaccharide derivative **79** was successfully obtained in 59% yield after

chromatography (Figure 3.10). In fact, the result is quite exciting, considering the poor reactivity of the accepter due to the steric effect of the surroundings. The stereochemistry of the newly formed anomeric center was verified by the coupling constant, $^{1}J_{C\text{-}1,\,H\text{-}1}$ = 168 Hz, which is consistent with the α-stereochemistry. The spectra were recorded in CD_2Cl_2 to avoid any degradation.

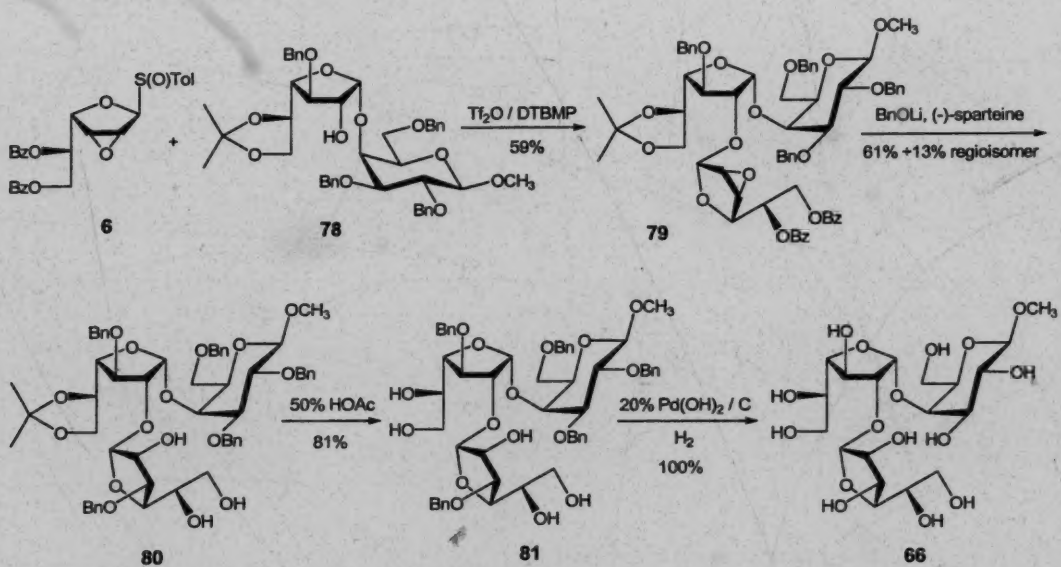


Figure 3.10. Synthesis of trisaccharide acceptor **66**.

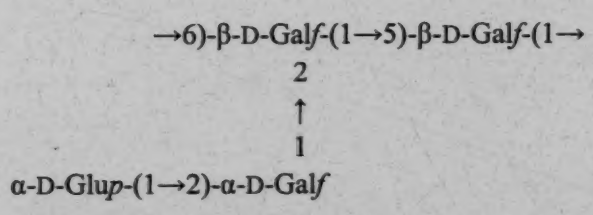
The epoxide functionality in compound **79** was then opened by the combined use of lithium benzylate and (-)-sparteine in overall 74% conversion, which gave the desired Gal*f* derivative in 61% yield after purification by chromatography. Compound **80** was subjected to 50% acetic acid solution (HOAc:H_2O:THF 5:3:2) at 50 °C for 12 hours to remove the isopropylidene ketal in 81% yield. The final target **66** was obtained in

quantitative yield after catalytic hydrogenolysis with Pearlman's catalyst to take off all the benzyl protecting groups.

A comparison between our synthesis and Ferrières and coworkers' IAD pathway, point out several advantages of our methodology. First, in the synthesis of the α-(1→4) linked disaccharide intermediate **77**, the overall yield of our synthesis is 50%, including glycosylation via 2,3-anhydro donors and the epoxide opening reaction. In contrast, the IAD process provides only 34% desired α-anomer. Secondly, we can directly obtain the 2-OH free disaccharide acceptor **78** for further glycosylation, while their method failed and only the disaccharide was synthesized.

3.5 Synthesis of the Pentasaccharide Repeating Unit of *Penicillium varians* Cell-Wall Polysaccharides

The extracellular polysaccharide, varianose, produced by *Penicillium varians*, was first identified and reported by Lindberg and co-workers in 1980.[112] A main structural element in the glucogalactan portion of the molecule is a tetrasaccharide unit having the structure:



The presence of both α- and β-D-galactofuranosyl residues in varianose is an unusual

feature. Interestingly, the same structural repeating unit was found in *Talaromyces flavus* strain 352 by Spanish chemists in 1994.[107] We selected pentasaccharide **67** as the synthetic target, which contains one repeating unit plus an addition β-galactofuranoside residue.

We planned to synthesize this pentasaccharide motif via a linear synthetic pathway, starting from reducing end unit A to pyranoside unit E (Figure 3.11). The building blocks include three galactofuranosyl intermediates (**6**, **82** and **83**) and a glucopyranoside derivative **84**. Donor **83** can be used for the installation of both residues B and C. All the building blocks can be prepared directly or indirectly from known compounds.

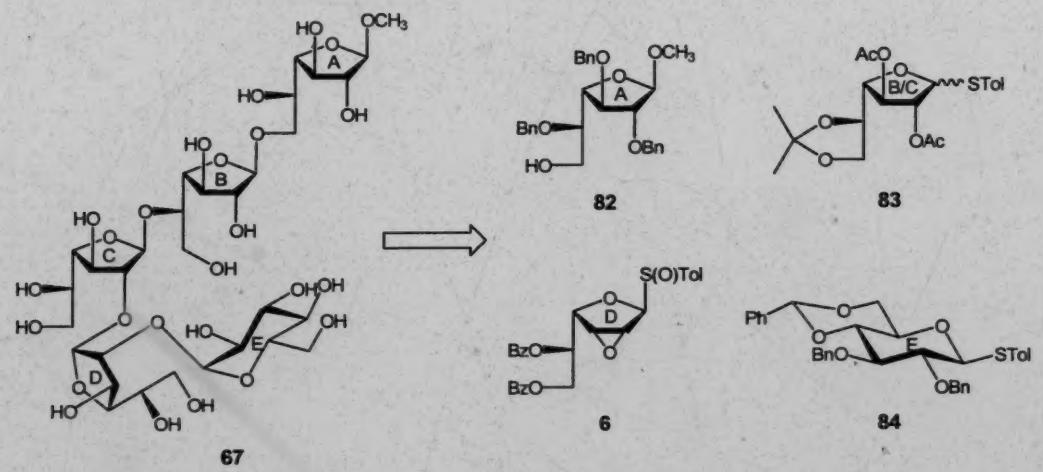


Figure 3.11. Retrosynthetic analysis of pentasaccharide motif **67**.

3.5.1 Synthesis of Building Blocks

Preparation of building blocks **82** and **83** was achieved in several steps from intermediates used in the synthesis of donor **1**. Thus, compound **85** was obtained in three

steps from the anomeric mixture of **8** (Figure 2.2) in 76% yield, after deacetylation, followed by tritylation and benzylation (Figure 3.12). The trityl moiety is a bulky protecting group, which can be selectively installed on a primary hydroxyl group; the addition of 4-dimethylaminopyridine (DMAP) catalyzes the reaction within 6 hours at 50 °C. The pure β-anomer **85** was isolated after benzylation of the remaining three hydroxyl groups. Removal of the trityl group was achieved by the addition of a catalytic amount of *p*-toluenesulfonic acid in dichloromethane and methanol to provide compound **82** in 86% yield.

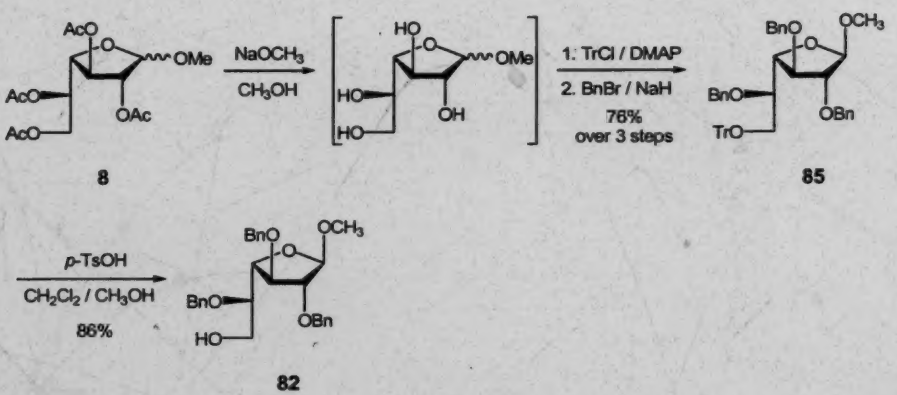


Figure 3.12. Synthesis of building block **82**.

Preparation of donor **83** was easier to reach, compared to the four-step synthesis of acceptor **82**. Starting from an anomeric mixture of **10** and **11** (Figure 2.3), protection of the 5- and 6-OH groups by an isopropylidene ketal and acylation of the 2- and 3-OH groups provided desired building block **83** in 84% yield (Figure 3.13). The acetyl

functionality on O-2 was chosen to guarantee the successful preparation of β-linkage in future glycosylations.

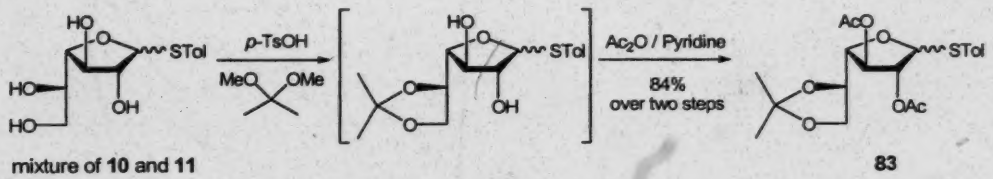


Figure 3.13. Synthesis of building block **83**.

Building block **84**[131] is a known compound, which was obtained as shown in the Figure 3.14. An anomeric mixture of D-glucose pentaacetate was converted into thio-glucopyranoside **86**[132] in 70% yield, using $BF_3 \cdot OEt_2$ and *p*-thiocresol. Deacylation of **86**, followed by the installation of benzylidene acetal provided known derivative **88**,[133] which was readily protected as a di-benzyl ether to give donor **84** in 92% yield.

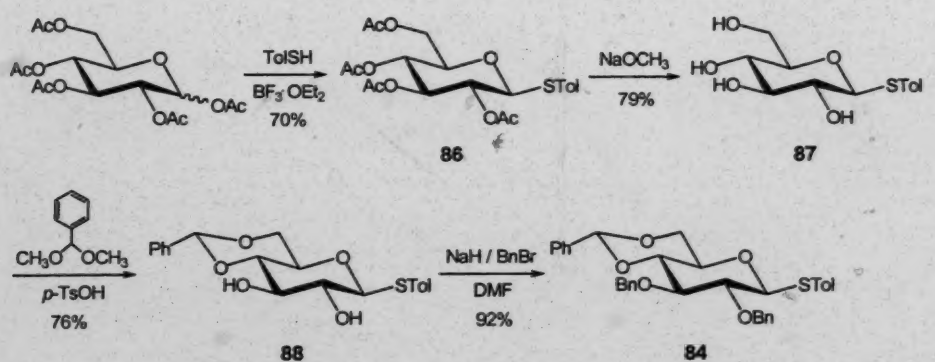


Figure 3.14. Synthesis of building block **84**.

3.5.2 Synthesis of Disaccharide Intermediate 92

With all the building blocks in hand, the disaccharide including units A and B was readily synthesized by coupling acceptor **82** with donor **83**. *N*-iodosuccinimide and silver triflate were added to the reaction mixture at -60 °Ç respectively, followed by the increase of the reaction temperature to 0 °C over a period of 30 minutes. The glycosylation reaction successfully afforded exclusively β-(1→6) linked disaccharide **89** in excellent 94% yield (Figure 3.15).

Considering the future use of basic conditions to open the oxarine ring in our methodology, the base-labile protecting group (*e.g.* Ac) was converted to base-stable benzyl ethers. Therefore, compound **89** was treated with $NaOCH_3/CH_3OH$ and then

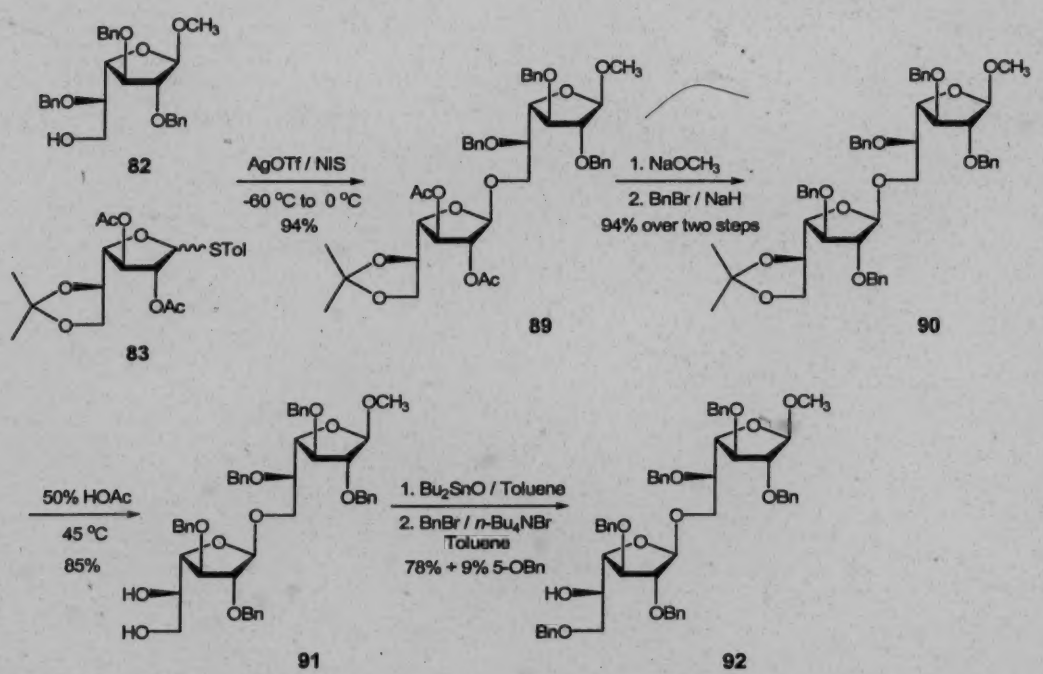


Figure 3.15. Synthesis of disaccharide intermediate **92**.

benzylation conditions (BnBr/NaH) to provide intermediate **90** in 94% yield. Subsequently, a 50% acetic acid solution at 45 °C was used to remove the isopropylidene ketal on O-5 and O-6.

Our next concern was the selective protection of 6-OH in **91** to produce an acceptor for synthesis of the trisaccharide. Several approaches were potentially applicable.

One approach would involve the use of bulky protecting groups that could be selectively introduced on the primary hydroxyl at C-6, such as a trityl (Tr) or a silyl group (TBDPS). However, regardless of their stability in future steps, the presence of bulky groups at C-6 may bring strong steric effects during glycosylation of 5-OH with donor **83**. Low yielding reactions at this stage should be avoided.

Another approach could be the introduction of an acyl group on O-5 after the tritylation or silylation of the 6-OH. Upon the removal of trityl moiety under acidic condition,[134] or silyl group using TBAF,[135] acyl migration[136] from O-5 to O-6 would produce a 6-*O*-acyl intermediate. However, this acyl group would be cleaved during the basic epoxide opening reaction in later stages.

A third approach was to selectively protect the 6-OH group as its benzyl ether. A thorough literature search indicated the possibility of this proposal using a stannylidene acetyl intermediate. The precursor **91** was converted into a dibutylstannylidene acetal by heating with Bu_2SnO in toluene at reflux followed by addition of 1.0 equivalent of BnBr to give the hexa-*O*-benzyl derivative **92** in 78% over two steps.[69] The regioselectivity of this method was very good, yielding the 6-OBn and 5-OBn derivatives in a 9:1 ratio.

3.5.3 Synthesis of Trisaccharide Intermediate 96

Donor **83** was employed in the glycosylation reaction with disaccharide derivative **92** to construct the β-(1→5) linkage. As before, the reaction was carried out starting from -60 °C and then gradually warmed to 0 °C. The color of the reaction mixture turned dark red after 30 minutes, and after usual work-up and chromatography, trisaccharide **93** was exclusively obtained in 89% yield. Both the acyl groups were subsequently removed when compound **93** was subjected to Zemplén deacylation.

The next concern was the regioselective protection of 3-OH, leaving the other secondary 2-OH intact. This problem could be probably solved by first introducing a pivaloyl ester on 2-OH, then benzylation of 3-OH, and deacylaction of the 2-OPiv group, a three-step conversion with a reported 50% overall yield.[100] However, this was not an ideal solution, and we sought an alternative approach. Mindful of the oxarine ring opening reactions with lithium benzylate, in which a benzyloxy group can be installed at C-3, we were inspired to attempt the protection of 3-OH via epoxide intermediate. After the formation of epoxide under modified Mitsunobu reaction conditions, treatment of **95** with lithium benzylate provided the desired trisaccharide acceptor **96** in 79% yield over two steps (Figure 3.16). In contrast to the other oxirane opening reactions studied in our methodology, exclusive regioselectivity was achieved in the opening of the 2,3-anhydro-β-D-gulofuranoside **95** even without the use of any additives. The result is probably due

to the bulky disaccharide moiety at the anomeric position introducing strong steric effect, leading to nucleophilic attack only at C-3.

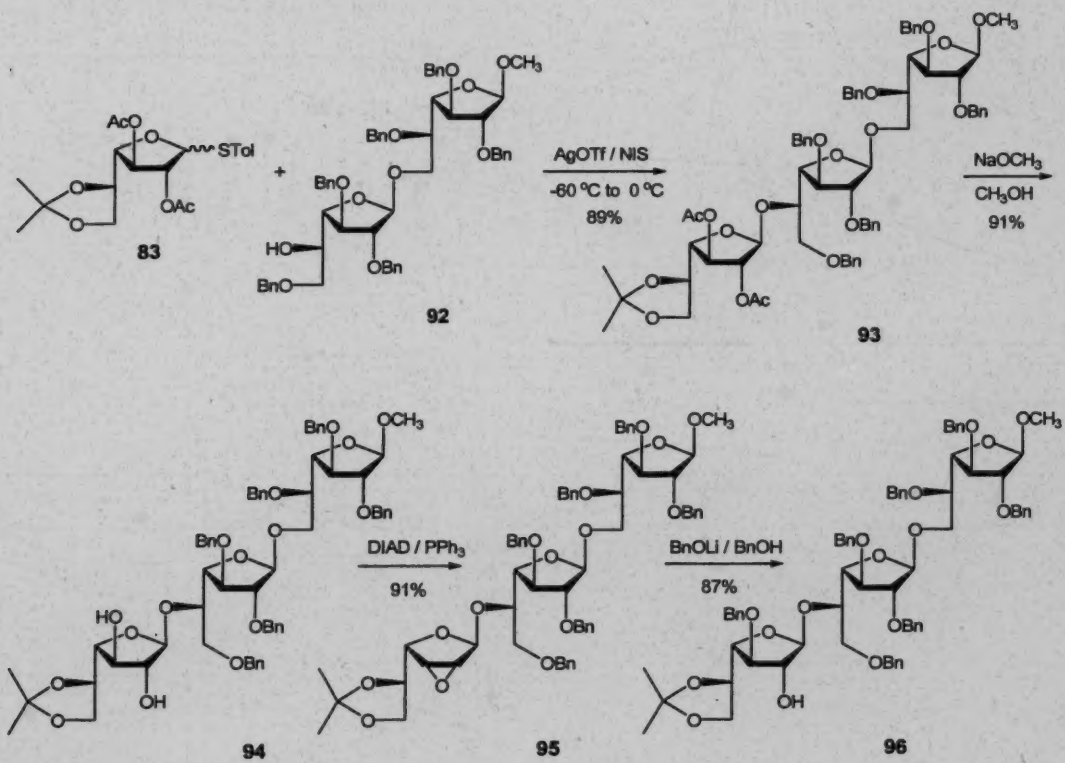


Figure 3.16. Synthesis of trisaccharide intermediate **96**.

NMR spectroscopy confirmed the formation of intermediate **95** and **96**. For compound **95**, two signals at 53.6 ppm and 55.6 ppm in the ^{13}C NMR spectrum verified the epoxide C-2 and C-3, which are both ~20 ppm upfield shifted compared to the signals of **94**. The coupling constant, $^{1}J_{C\text{-}1,\,H\text{-}1}$ = 176 Hz, measured through a coupled GHMQC-2D experiment, gave strong evidence that the newly formed oxirane ring is *trans* to the existing β-glycosidic bond in epoxide **95**. Meanwhile, in the ^{1}H NMR spectrum of

compound **96**, the coupling constant, $^{3}J_{H\text{-}1,\,H\text{-}2} = 0$ Hz, proved that the newly formed free hydroxyl group at C-2 in the epoxide opening reaction is *trans* to the existing β-glycosidic linkage, and that the 2,3-anhydro species was transformed back to Gal*f* stereochemistry.

3.5.4 Synthesis of Tetrasaccharide Intermediate 99

Previous attempts in the synthesis of trisaccharide motif **66** of the polysaccharide generated by *E.saburreum T19* suggested that thioglycoside **5** is not a suitable

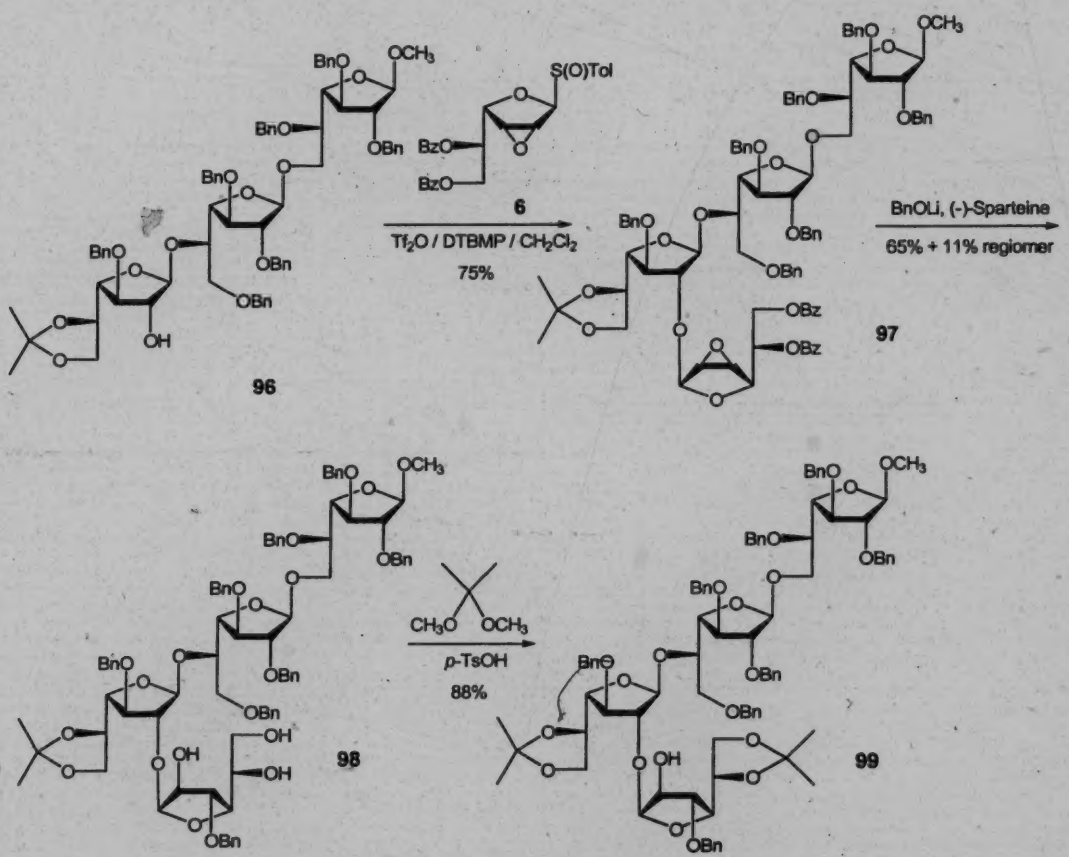


Figure 3.17. Synthesis of tetrasaccharide intermediate **99**.

glycosylating agent if an acid-labile 5,6-*O*-isopropylidene group is present in the glycosyl acceptor. In contrast, glycosylation via sulfoxide **6** was carried out efficiently under neutral conditions. Therefore, sulfoxide-mediated coupling was employed and the α-(1→2) linked tetrasaccharide **97** was obtained in 75% yield (Figure 3.17). The coupling constant, $^{1}J_{C\text{-}1,\ H\text{-}1}$=167 Hz, measured from coupled GHMQC-2D spectrum proved the stereochemistry of the new glycosidic bond, which is *cis* to the oxirane ring.

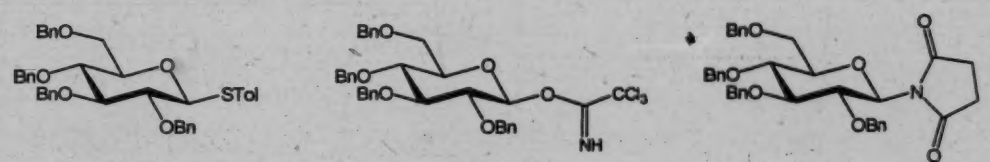
Treatment of α-D-gulofuranoside **97** in the presence of (-)-sparteine and lithium benzylate afforded separable tetrasaccharide derivative **98** and its regioisomer in a 6:1 ratio in 76% overall yield. Finally, the isopropylidene ketal was installed to protect the hydroxyl groups at C-5 and C-6, providing acceptor **99** in 88% yield. The free hydroxyl group at C-2 of **99** was available for further elaboration through glycosylation.

3.5.5 Synthesis of Pentasaccharide Target 67

The installation of the final glucopyranosyl residue (ring E) at C-2 of tetrasaccharide **99** was not a straightforward proposition. To prepare 1,2-*cis*-α-glycosides, the use of non-participating groups on C-2 is required. In nonpolar solvents (*e.g.*, CH_2Cl_2) and under normal reaction conditions, 2-*O*-alkylated glycosyl donors give predominantly α-glycosides due to the kinetic anomeric effect.[137]

Therefore, we first employed tetra-*O*-benzyl thioglycoside **100**[138] as the glycosyl donor in the coupling with tetrasaccharide acceptor **99**. *N*-iodosuccinimide and a catalytic amount of silver triflate were added to a solution of **99** and **100** in CH_2Cl_2 at -60 °C.

After the reaction was warmed to 0 °C and the solution color changed to deep red, TLC monitoring of the reaction showed the absence of glycosyl donor and two newly formed major spots. After isolation and characterization of those two compounds, one was identified as acceptor **99** and the other was the succinimide adduct **102**. Similar succinimide derivatives have been previously reported,[130] which, in most cases, can be explained by the low reactivity of the glycosyl acceptors. In our case, the highly hindered 2-OH makes **99** much less reactive, even less than the succinimide in the solution.



100 **101** **102**

Figure 3.18. Unsuccessful glucopyranosyl donors attempted and succinimide adduct **102**.

Alternatively, we prepared the known imidate donor **101**.[32] A model study with 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranoside indicated that this reactive imidate is not an efficient donor to couple with unreactive acceptors. Another issue was that the acidic activation conditions are potentially not compatible with the two isopropylidene ketals attached to acceptor **99**, which may be cleaved during the reaction.

Crich's BSP/Tf_2O activation method for thioglycosides attracted our attention because of several advantages. First, the neutral reaction condition is not problematic with the ketal moiety. Second, the activation involves *in situ* formation of glycosyl triflate intermediate, which are rapidly converted to glycosides in a S_N2 type displacement with

good selectivity. Third, no good nucleophile other than the acceptor is introduced to the reaction mixture, so that any competing reactions might be prevented.

Preparation of donor **84** has been outlined in a previous section (Figure 3.14). Donor **84** was treated with triflic anhydride in the presence of 1-benzenesulfinyl piperidine (BSP) and 2,4,6-tri-*tert*-butylpyrimidine (TTBP) in CH_2Cl_2 at -60 °C. The mixture was allowed to stir at -60 °C for 10 minutes, followed by the addition of acceptor **99**. After the mixture

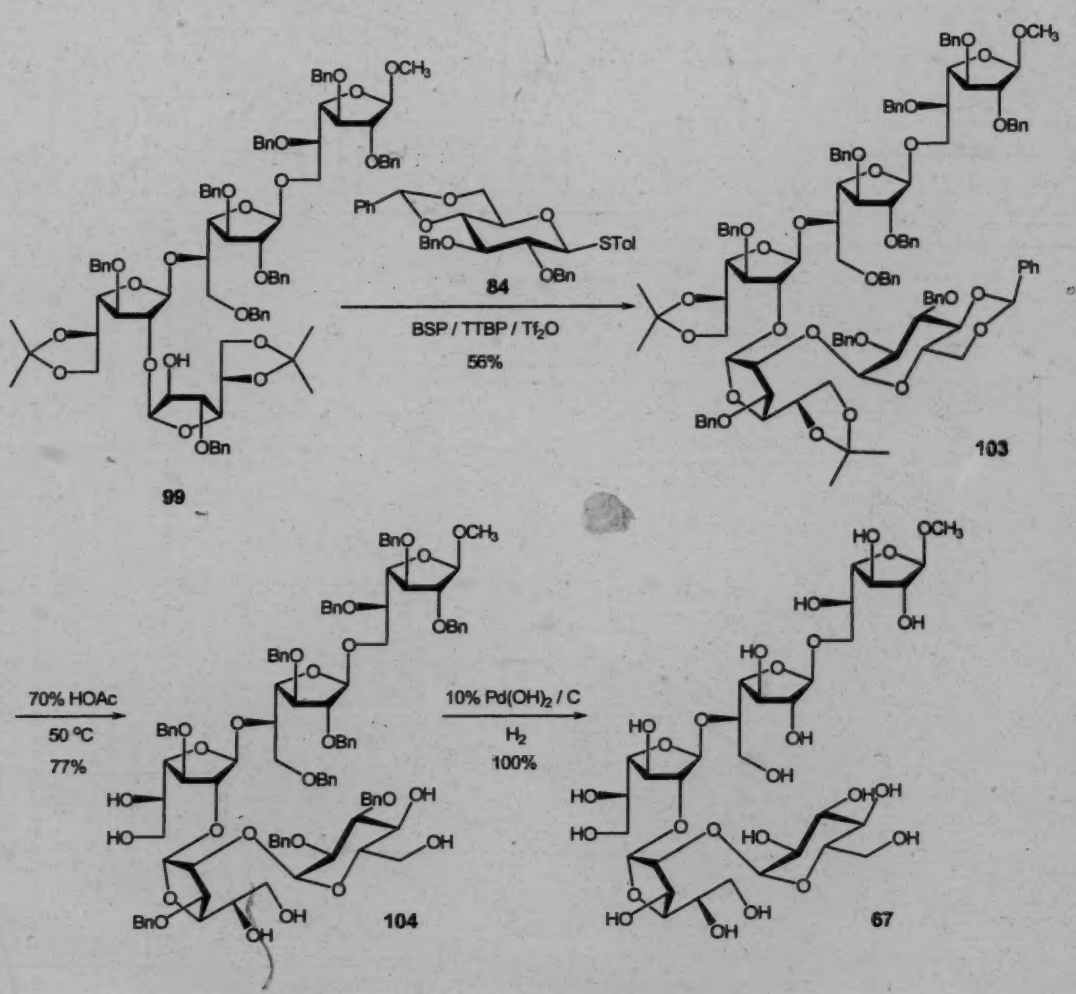


Figure 3.19. Synthesis of pentasaccharide target **67**.

was warmed to room temperature and kept for 48 hours, pentasaccharide **103** was successfully obtained after chromatography. The 56% yield was excellent and much better than we expected, considering the extremely hindered hydroxyl on **99**. The α-stereochemistry of the anomeric center was proved by the anomeric proton signal, which appeared as a doublet at 5.11 ppm with a coupling constant value $^{3}J_{H\text{-}1,\,H\text{-}2} = 3.6$ Hz.

Pentasaccharide intermediate **103** was subjected to a 70% acetic acid solution at 50 °C to remove the two isopropylidene ketals together with the benzylidene acetal. Catalytic hydrogenolysis of **104** provided the desired final pentasaccharide motif **67** in quantitative yield (Figure 3.19).

3.6 Conclusion

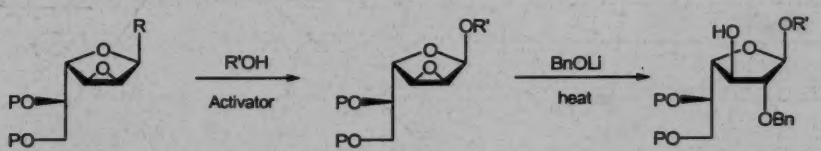
We have successfully employed the 2,3-anhydrosugars in the synthesis of oligosaccharide motifs of natural polysaccharides. The yields and selectivities obtained in these reactions are comparable to or better than existing methods.

3.7 Future work

The reaction conditions for the nucleophilic ring opening reactions of epoxide moiety need to be optimized, and the mechanism of the regioselectivity observed in these reactions is necessary to be explored further.

We are currently unsure as to the origin of the remarkable stereoselectivity in the glycosylation reactions of 2,3-anhydro thioglycoside donors. Further investigation is necessary for a better understanding of the mechanisms of these reactions.

Furthermore, development of an efficient synthesis of 2,3-anhydro-β-D-talo-furanosyl thioglycoside **105** and sulfoxide **106** will help us to study their potential application in the synthesis of oligosaccharides containing β-D-galactofuranosyl residues, which are widespread in nature.



105 R = STol
106 R = S(O)Tol

Figure 3.20. General scheme for the synthesis of β-D-galactofuranoside via 2,3-anhydrosugar

CHAPTER 4

EXPERIMENTAL PROCEDURES

4.1 General Methods.

All reagents used were purchased from commercial sources and were used without further purification unless noted. Solvents used in reactions were purified by PURESOLV-400 System from Innovative Technology Inc.. Unless stated otherwise, all reactions were carried out under a positive pressure of argon and were monitored by TLC on silica gel G-25 UV_{254} (0.25 mm, Macherey-Nagel). Spots were detected under UV light and/or by charring with 10% H_2SO_4 in ethanol, or in acidified ethanolic anisaldehyde. Solvents were evaporated under reduced pressure and below 50 °C (water bath). Column chromatography was performed on silica gel 60 (40-60 mM). The ratio between silica gel and crude product ranged from 100:1 to 20:1 (w/w). Melting points were recorded on an eletrothermal melting point apparatus. ^1H NMR spectra were recorded on VARIAN INOVA-NMR spectrometers at 400, 500 or 600 MHz, and chemical shifts are referenced to either TMS (0.0, $CDCl_3$) or CD_3OD (4.78, CD_3OD). ^{13}C NMR spectra were recorded at 100 or 125 MHz, and ^{13}C chemical shifts are referenced to $CDCl_3$ (77.23, $CDCl_3$) or CD_3OD (48.9, CD_3OD). ^1H NMR data are reported as though they are first order, and the peak assignments were made by 2D-NMR spectroscopy.

ESI-MS spectra were recorded on samples suspended in THF or CH_3OH and added NaCl. Optical rotations were measured on Perkin-Elmer 241 Polarimeter with sodium D line (589 nm). Optical rotations are in units of deg·ML(dm·g)$^{-1}$.

4.2 General Procedures for Glycosylations with 2,3-Anhdrosugar Donors

4.2.1 Activation of Thioglycoside Donors by the AgOTf/NIS Method

The donor (0.1 mmol), acceptor (1.2 equiv.) and 4 Å molecular sieves were dried overnight under vacuum in the presence of P_2O_5. To this mixture was added CH_2Cl_2 (5 mL) and the reaction was cooled to –40 °C and then *N*-iodosuccinimide (1.2 equiv.) and silver triflate (0.3 equiv.) was successively added. After stirring for 20 min at –40 °C, the reaction solution was warmed to –25 °C. Once the color of the reaction was changed to pink, it was cooled back to –40 °C again. After another 30 min, the reaction mixture turned dark red, and was then neutralized by addition of triethylamine, diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with sat. aq. $Na_2S_2O_3$ soln., dried (Na_2SO_4), and concentrated to give a crude residue that was purified by chromatography to yield the corresponding separable α (major) and β (minor) glycosides.

4.2.2 Activation of Thioglycoside Donors by the BSP/Tf_2O Method

The donor (0.1 mmol), 1-benzenesulfinyl piperidine (1.0 equiv.), 2,4,6-tri-*tert*-butyl-pyrimidine (2.0 equiv.), and 4 Å molecular sieves were dried for 4 h under vacuum in the

presence of P_2O_5. To this mixture was added CH_2Cl_2 (5 mL) and the reaction mixture was cooled to –60 °C. Triflic anhydride (1.1 equiv.) was added and the mixture was allowed to stir for 10 min, followed by the addition (via syringe) of a solution of the vacuum dried acceptor (1.1 equiv.) in CH_2Cl_2. After 40 min, the reaction mixture was warmed to room temperature and kept stirring for 12 h. A saturated solution of $NaHCO_3$ was added and the resulting solution was filtered through Celite, dried, filtered, and concentrated to yield a crude oil that was purified by chromatography.

4.2.3 Activation of Sulfoxide Donors by the Tf_2O/DTBMP Method

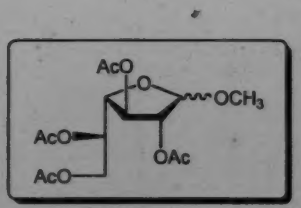
The donor (0.1 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (4.0 equiv.), and 4 Å molecular sieves were dried overnight under vacuum in the presence of P_2O_5. To this mixture was added CH_2Cl_2 (5 mL) and the reaction mixture was cooled to –78 °C. Triflic anhydride (1.2 equiv.) was added and the mixture was allowed to stir for 10 min. The solution was then warmed to –40 °C and stirred for 20 min followed by the addition of acceptor alcohol (1.2 equiv.). After 30 min to 60 min, the reaction mixture turned slight green and a salturated solution of $NaHCO_3$ was then added and the solution was allowed to warm to room temperature. The resulting solution was filtered through Celite, dried, filtered, and concentrated to yield a crude oil that was purified by chromatography to give the corresponding α-glycosides.

4.3 General Procedure for Epoxide Opening Reactions

To a solution of benzyl alcohol (3.0 mL) was added lithium metal (6.0 mmol) and the solution was stirred at 65 °C until all the metal dissolved. After cooling to room temperature, the mixture was added together with an additive (1.2 mmol) via syringe to a solution of the epoxide (1.0 mmol) dissolved in benzyl alcohol (0.5 mL). The resulting mixture was subsequently warmed to 75 °C and allowed to stir until the reaction was complete. After cooling to room temperature, the solution was neutralized with acetic acid and diluted with EtOAc (10 mL). The organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated to give a crude residue that was purified by chromatography. Those reactions done in the absence of an additive were carried out in an analogous manner. (Additive = (-)-sparteine or tetramethylpropyldiamine (TMPDA)).

4.4 Experimental Procedures and Characterization of New Compounds

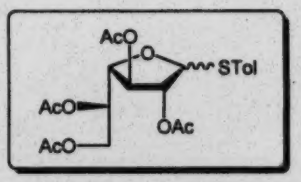
Methyl 2,3,5,6-tetra-*O*-acetyl-α/β-D-galactofuranoside (8).



D-Galactose diethyl dithioacetal **7** (10.0 g, 35.0 mmol) was dissolved in 2% I_2 (10.0 g) solution in methanol (500 mL) and stirred for 7 h at room temperature. $NaHCO_3$ and $Na_2S_2O_3$ solids were added to neutralize the solution, followed by concentration to give a crude sticky syrup. The crude mixture was subsequently dissolved in pyridine (60 mL) and

cooled to 0 °C. Acetic anhydride (40 mL, 0.42 mol) was added, and the solution was allowed to stand for 14 h at room temperature. The reaction mixture was then poured into ice water (200 mL) containing $NaHCO_3$ (20.0 g), and extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated to yield the crude product. Chromatography (2:1, hexane:EtOAc) yielded **8** (10.7 g, 85% over two steps) as a colorless oil. R_f 0.43 (1:1, hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 5.57 (t, 0.35 H, J = 6.8 Hz, H-3α), 5.38 (ddd, 0.65 H, J = 8.1, 4.4, 4.4 Hz, H-5β), 5.30 (s, 0.35 H, H-1α), 5.24-5.19 (m, 0.35 H, H-5α), 5.07-4.99 (m, 1.65 H, H-2β, H-3β, H-2α), 4.92 (s, 0.65 H, H-1β), 4.36 (dd, 0.35 H, J = 9.5, 4.5 Hz, H-6α), 4.33 (dd, 0.65 H, J = 12.0, 4.5 Hz, H-6β), 4.25-4.09 (m, 2 H, H-4α, H-4β, H-6α, H-6β), 3.39 (s, 1.95 H, OC$\underline{H}_3$β), 3.37 (s, 1.05 H, OC$\underline{H}_3$α), 2.14 (s, 1.95 H, COC$\underline{H}_3$β), 2.13 (s, 1.05 H, COC$\underline{H}_3$α), 2.11 (s, 3 H, COC$\underline{H}_3$α, COC$\underline{H}_3$β), 2.09 (s, 1.95 H, COC$\underline{H}_3$β), 2.07 (s, 1.05 H, COC$\underline{H}_3$α), 2.06 (s, 1.95 H, COC$\underline{H}_3$β), 2.05 (s, 1.05 H, COC$\underline{H}_3$α); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 170.48 (C=O), 170.38 (C=O), 169.99 (C=O × 2), 169.96 (C=O × 2), 169.78 (C=O), 169.63 (C=O), 106.61 (C-1β), 100.52 (C-1α), 81.33 (C-2β), 79.87 (C-4β), 77.73 (C-4α), 76.52 (C-3β), 76.38 (C-3α), 73.57 (C-2α), 70.62 (C-5α), 69.29 (C-5β), 62.59 (C-6β), 62.24 (C-6α), 55.31 (O$\underline{C}H_3$α), 54.97 (O$\underline{C}H_3$β), 20.82 (CO$\underline{C}H_3$), 20.79 (CO$\underline{C}H_3$), 20.74 (CO$\underline{C}H_3$), 20.69 (CO$\underline{C}H_3$), 20.66 (CO$\underline{C}H_3$ × 2), 20.65 (CO$\underline{C}H_3$ × 2). HRMS (ESI) calcd. for (M+Na) $C_{15}H_{22}O_{10}Na$ 385.1104, found 385.1105.

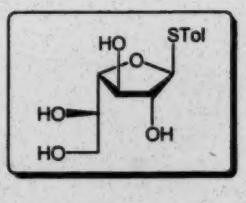
***p*-Tolyl 2,3,5,6-tetra-*O*-acetyl-1-thio-α/β-D-galactofuranoside (9).**



To a solution of *p*-thiocresol (2.24 g, 17.7 mmol) and **8** (5.82 g, 16.1 mmol) in dry CH_2Cl_2 (80 mL) was added BF_3-etherate (6.1 mL, 48.2 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and then diluted with CH_2Cl_2 (100 mL), washed with a sat. aq. $NaHCO_3$ soln (3 × 150 mL), dried (Na_2SO_4), and concentrated. Chromatography (4:1, hexane: EtOAc) yielded **9** (5.51 g, 76%) in a 1:9 α:β ratio as a slightly yellow syrup. R_f 0.37 (4:1, hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.41-7.36 (m, 2 H, Ar), 7.12 (d, 2 H, J = 7.9 Hz, Ar), 5.52 (d, 0.1 H, J = 5.2 Hz, H-1α), 5.46 (dd, 0.1 H, J = 5.2, 3.8 Hz, H-2α), 5.43 (d, 0.9 H, J = 2.5 Hz, H-1β), 5.40-5.35 (m, 1 H, H-5α, H-5β), 5.31 (dd, 0.1 H, J = 5.0, 3.8 Hz, H-3α), 5.21 (dd, 0.9 H, J = 2.7, 2.5 Hz, H-2β), 5.04 (dd, 0.9 H, J = 6.1, 2.7 Hz, H-3β), 4.46 (dd, 0.9 H, J = 6.1, 3.8 Hz, H-4β), 4.40 (dd, 0.1 H, J = 12.0, 4.1 Hz, H-6α), 4.32 (dd, 0.9 H, J = 11.8, 4.6 Hz, H-6β), 4.22-4.18 (m, 0.1 H, H-6α), 4.18 (dd, 0.9 H, J = 11.8, 6.1 Hz, H-6β), 4.08 (dd, 0.1 H, J = 5.1, 5.0 Hz, H-4α), 2.33 (s, 3 H, tolyl CH_3), 2.17 (s, 0.3 H, acyl CH_3α), 2.14 (s, 0.3 H, acyl CH_3α), 2.11 (s, 2.7 H, acyl CH_3β), 2.10 (s, 5.7 H, acyl CH_3), 2.07 (s, 0.3 H, acyl CH_3α), 2.40 (s, 2.7 H, acyl CH_3β); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.44 (C=O), 169.95 (C=O), 169.87 (C=O), 169.56 (C=O), 138.27 (Ar), 138.02 (Ar), 132.95 (Ar × 2), 132.69 (Ar × 2), 129.85 (Ar × 2), 129.77 (Ar × 2), 129.20 (Ar × 2), 90.68 (C-1β), 89.56 (C-1α), 81.21 (C-2β), 80.55 (C-2α), 79.55 (C-4β), 76.99 (C-4α), 76.51 (C-3β), 75.93 (C-3α), 69.73 (C-5α), 69.07 (C-5β), 62.56 (C-6α), 62.51 (C-6β), 21.12 (tolyl CH_3), 20.77 (acyl CH_3), 20.73 (acyl CH_3), 20.67 (acyl

CH_3), 20.66 (acyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{14}H_{28}O_6Na$ 477.1190, found 477.1194.

***p*-Tolyl 1-thio-β-D-galactofuranoside (10).**

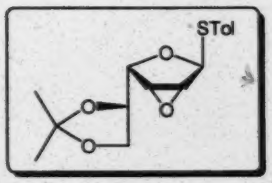


To a solution of **9** (4.76 g, 10.5 mmol) in CH_3OH (100 mL) and CH_2Cl_2 (100 mL) was added solid $NaOCH_3$ until the pH was ~10. The solution was allowed to stir at room temperature for 4 h and then neutralized with acetic acid. The mixture was concentrated and the resulting crude was purified by chromatography (10:1, CH_2Cl_2:CH_3OH), to yield the anomers **10** (2.41 g, 80%) and **11** (0.25 g, 8%) as white solids. Data for **10**: R_f 0.21 (10:1, CH_2Cl_2:CH_3OH); $[\alpha]_D$ –231.1 (*c* 0.8, CH_3OH). ^1H NMR (400 MHz, CD_3OD, δ_H) 7.42-7.38 (m, 2 H, Ar), 7.14-7.10 (m, 2 H, Ar), 5.15 (d, 1 H, J = 5.0 Hz, H-1), 4.07 (dd, 1 H, J = 7.6, 5.4 Hz, H-3), 3.96-3.10 (m, 2 H, H-2, H-4), 3.71 (ddd, 1 H, J = 6.9, 5.9, 2.9 Hz, H-5), 3.62-3.58 (m, 2 H, H-6 × 2), 2.30 (s, 3 H, tolyl CH_3); ^{13}C NMR (100 MHz, CD_3OD, δ_C) 138.76 (Ar), 133.67 (Ar × 2), 132.23 (Ar), 130.58 (Ar×2), 93.28 (C-1), 83.12 (C-2), 83.03 (C-4), 77.75 (C-3), 72.03 (C-5), 64.55 (C-6), 21.12 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{13}H_{18}O_5SNa$ 309.0767, found 309.0764.

***p*-Tolyl 2,3-anhydro-5,6-*O*-isopropylidene-1-thio-β-D-gulofuranoside (1).**

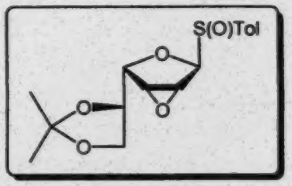
To a solution of **10** (2.15 g, 7.52 mmol) and 2,2-dimethoxypropane (7.4 mL, 60.1 mmol) in acetone (50 mL) was added *p*-toluenesufonic acid (7 mg, cat.) at room temperature.

The solution was allowed to stir for 2 h, and neutralized with triethylamine. TLC showed a spot at R_f 0.40 (15:1, CH_2Cl_2: CH_3OH). The mixture was concentrated and the resulting oil



was dissolved in THF (40 mL) followed by the addition of PPh_3 (2.57 g, 9.78 mmol). DIAD (1.9 mL, 9.78 mmol) was then added dropwise at 0 °C over the course of 10 min. The reaction mixture was allowed to warm to room temperature over the course of 30 min. The resulting mixture was concentrated and diethyl ether (60 mL) was added to precipitate the $Ph_3P=O$, which was subsequently removed by filtration. The organic layer was concentrated and the residue was purified by chromatography (6:1, hexanes:EtOAc) to yield **1** (1.87 g, 81% over two steps) as a white solid. R_f 0.46 (4:1, hexanes:EtOAc); m.p. 76-78 °C; $[\alpha]_D$ –187.1 (*c* 1.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.45-7.41 (m, 2 H, Ar), 7.13-7.11 (m, 2 H, Ar), 5.48 (s, 1 H, H-1), 4.32 (dd, 1 H, J = 12.6, 6.3 Hz, H-5), 4.06 (dd, 1 H, J = 8.6, 6.3 Hz, H-6), 4.01-3.97 (m, 2 H, H-4, H-6), 3.88 (d, 1 H, J = 2.9 Hz, H-2), 3.67 (dd, 1 H, J = 2.9, 0.5 Hz, H-3), 2.34 (s, 3 H, tolyl CH_3), 1.47 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 138.35 (Ar), 133.47 (Ar × 2), 129.88 (Ar), 128.62 (Ar × 2), 109.71 (isopropylidene C), 87.27 (C-1), 77.04 (C-4), 74.58 (C-5), 65.59 (C-6), 56.80 (C-2), 54.91 (C-3), 26.64 (isopropylidene CH_3), 21.13 (isopropylidene CH_3), 21.13 (tolyl CH_3). Anal. Calcd for $C_{16}H_{20}O_4S$: C, 62.31, H, 6.54, found: C, 62.09, H, 6.68. HRMS (ESI) calcd. for (M+Na) $C_{16}H_{20}O_4SNa$ 331.0975, found 331.0976.

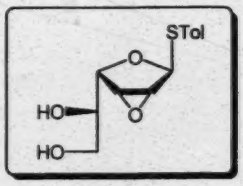
2,3-anhydro-5,6-*O*-isopropylidene-β-D-gulofuranosyl-*p*-tolyl(R/S)-sulfoxide (2a/2b).



To a solution of **1** (620 mg, 2.0 mmol) in CH_2Cl_2 (40 mL) was added *m*-CPBA (430 mg, 1.8 mmol) at –78 °C. After stirring for 2 h, the reaction mixture was warmed to room temperature and stirred for 30 min. The solution was washed with a sat. aq. solution of $NaHCO_3$ (3 × 30 mL) and then water (3 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to yield a crude oil that was purified by chromatography (8:1, hexanes: EtOAc) to provide the diastereomers **2a** (380 mg, 71%) and **2b** (160 mg, 13%) as white semi-solids. **2a**: R_f 0.32 (1:1, hexanes:EtOAc); $[\alpha]_D$ +216.0 (*c* 1.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.50 (d, 2 H, J = 8.2 Hz, Ar), 7.38 (d, 2 H, J = 8.5 Hz, Ar), 4.74 (s, 1 H, H-1), 4.43 (dd, 1 H, J = 7.1, 0.7 Hz, H-4), 4.27 (q, 1 H, J = 6.5 Hz, H-5), 4.09 (dd, 1 H, J = 8.5, 6.5 Hz, H-6), 3.94 (d, 1 H, J = 2.9 Hz, H-2), 3.93 (dd, 1 H, J = 8.5, 6.5 Hz, H-6), 3.84 (dd, 1 H, J = 2.9, 0.7 Hz, H-3), 2.44 (s, 3 H, tolyl CH_3), 1.48 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 142.07 (Ar), 136.42 (Ar), 130.25 (Ar × 2), 124.09 (Ar × 2), 110.07 (isopropylidene C), 96.33 (C-1), 80.96 (C-4), 74.89 (C-5), 65.45 (C-6), 55.48 (C-3), 54.48 (C-2), 26.65 (isopropylidene CH_3), 25.20 (isopropylidene CH_3), 21.43 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{16}H_{20}O_5SNa$ 347.0924, found 347.0926. **2b**: R_f 0.20 (1:1, hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.58-7.54 (m, 2 H, Ar), 7.37-7.33 (m, 2 H, Ar), 4.88 (s, 1 H, H-1), 4.23-4.16 (m, 3 H, H-4, H-5, H-2), 4.02 (dd, 1 H, J = 8.5, 6.5 Hz, H-6), 3.86 (dd, 1 H, J = 8.5, 5.5 Hz, H-6), 3.72 (dd, 1 H, J = 2.9, 0.7 Hz, H-3), 2.44 (s, 3 H, tolyl CH_3),

1.45 (s, 3 H, isopropylidene CH_3), 1.34 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 142.35 (Ar), 136.04 (Ar), 130.02 (Ar), 129.95 (Ar), 125.34 (Ar × 2), 109.90 (isopropylidene C), 94.35 (C-1), 81.73 (C-4), 74.89 (C-5), 65.37 (C-6), 55.82 (C-2), 55.70 (C-3), 26.68 (isopropylidene CH_3), 25.17 (isopropylidene CH_3), 21.52 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{16}H_{20}O_5SNa$ 347.0924, found 347.0922.

_p_-Tolyl 2,3-anhydro-1-thio-β-D-gulofuranoside (14).

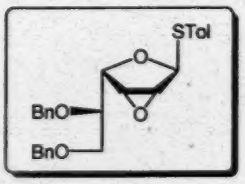


To a solution of **10** (1.95 g, 6.82 mmol) and trimethyl orthoacetate (1.0 mL, 8.1 mmol) in THF (50 mL) was added *p*-toluenesufonic acid (0.025 g, cat.) at room temperature. The solution was stirred for 3 h and then neutralized with triethylamine. TLC showed two new spots at R_f 0.50 (major) and 0.42 (minor) (10:1, CH_2Cl_2:CH_3OH). The mixture was then cooled to 0 °C, followed by addition of PPh_3 (7.15 g, 27.3 mmol). DIAD (5.6 mL, 27.3 mmol) was subsquently added dropwise at 0 °C over 10 min. The reaction mixture was allowed to warm to room temperature over 60 min. TLC showed one major new spot at R_f 0.45 (4:1 hexanes:EtOAc). The reaction mixture was concentrated and redissolved in EtOAc (200 mL), followed by washing with 0.3% HCl aq. soln. (100 mL) until the previous spot disappeared and two new spots formed at R_f 0.28 (major) and 0.20 (minor) (15:1, CH_2Cl_2: CH_3OH), which were the corresponding 5-*O*-acetyl and 6-*O*-acetyl mixture. The solution was dried (Na_2SO_4), filtered, and concentrated to give a yellow oil. To the solution of the crude mixture in CH_3OH (50 mL) and CH_2Cl_2 (50 mL) was added solid $NaOCH_3$ until

the pH was ~10. The solution was stirred at room temperature for 14 h, followed by neutralization with acetic acid. The resulting mixture was concentrated and purified by chromatography (2:1, hexanes:EtOAc), to yield **14** (1.32 g, 72% over four steps) as a colorless oil. R_f 0.21 (2:1, hexanes:EtOAc); $[\alpha]_D$ –19.1 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 7.45-7.42 (m, 2 H, Ar), 7.15-7.12 (m, 2 H, Ar), 5.45 (s, 1 H, H-1), 3.93 (dd, 1 H, J = 6.2, 0.7 Hz, H-4), 3.92 (d, 1 H, J = 2.9 Hz, H-2), 3.82 (dd, 1 H, J = 2.9, 0.7 Hz, H-3), 3.79 (ddd, 1 H, J = 6.2, 6.2, 4.4 Hz, H-5), 3.66 (dd, 1 H, J = 11.6, 4.4 Hz, H-6), 3.61 (dd, 1 H, J = 11.6, 6.2 Hz, H-6), 2.31 (s, 3 H, tolyl CH_3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 139.42 (Ar), 134.51 (Ar × 2), 130.82 (Ar × 2), 130.55 (Ar), 88.28 (C-1), 79.16 (C-4), 72.82 (C-5), 64.63 (C-6), 58.26 (C-2), 56.20 (C-3), 21.14 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{13}H_{16}O_4SNa$ 291.0662, found 291.0660.

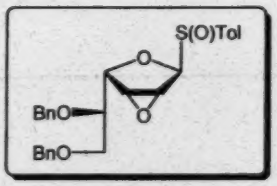
***p*-Tolyl 2,3-anhydro-5,6-di-*O*-benzyl-1-thio-β-D-gulofuranoside (2).**

To a solution of **14** (60 mg, 0.22 mmol) in DMF (1.5 mL) at 0 °C was added NaH (3 mg, 0.72 mmol, 60% dispersion in oil) and the mixture was stirred for 5 min. Benzyl bromide (64 μL, 0.54 mmol) was added dropwise at 0 °C and the mixture was stirred for 6 h at room temperature. The reaction mixture was then quenched by adding a few drops of CH_3OH, diluted with CH_2Cl_2 (10 mL), and washed with sat. aq. $NaHCO_3$ soln. (3 × 10 mL) and water (3 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated, and the resulting residue was purified by chromatography (4:1 hexanes:EtOAc) to provide **2** (93 mg, 93%)



as a colorless oil. R_f 0.52 (4:1, hexanes:EtOAc); $[\alpha]_D$ –127.6 (*c* 1.2, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.46-7.43 (m, 2 H, Ar), 7.38-7.27 (m, 10 H, Ar), 7.13 (d, 2 H, J = 7.9 Hz, Ar), 5.50 (s, 1 H, H-1), 4.76 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.71 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.59 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.54 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.21 (d, 1 H, J = 6.3 Hz, H-4), 3.88-3.83 (m, 1 H, H-5), 3.84 (d, 1 H, J = 2.9 Hz, H-2), 3.77-3.70 (m, 3 H, H-3, H-6×2), 2.38 (s, 3 H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.63 (Ar), 138.19 (Ar), 138.15 (Ar), 133.33 (Ar × 2), 129.81 (Ar × 2), 129.06 (Ar), 128.37 (Ar × 2), 128.26 (Ar × 2), 127.84 (Ar × 2), 127.65 (Ar × 2), 127.61 (Ar), 127.53 (Ar), 86.98 (C-1), 77.68 (C-5), 77.51 (C-4), 73.49 ($PhCH_2$), 73.14 ($PhCH_2$), 70.82 (C-6), 56.89 (C-2), 55.40 (C-3), 21.14 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{27}H_{28}O_4SNa$ 471.1601, found 471.1600.

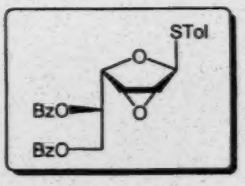
2,3-anhydro-5,6-di-*O*-benzyl-β-D-gulofuranosyl-*p*-tolyl(R/S)-sulfoxide (4a/4b).



To a solution of **3** (410 mg, 0.91 mmol) in CH_2Cl_2 (25 mL) at –78 °C was added *m*-CPBA (0.20 g, 0.82 mmol). After stirring for 2 h, the reaction mixture was warmed to room temperature and stirred for 30 min. The solution was washed with a sat. aq. solution of $NaHCO_3$ (3 × 15 mL) and then water (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to yield a crude oil that was purified by chromatography (3:1, hexanes: EtOAc) to provide the diastereomers **4a** (220 mg, 58%) and **4b** (110 mg, 29%) as white semi-solids. **4a**: R_f 0.27 (2:1, hexanes:EtOAc); $[\alpha]_D$ +104.4 (*c* 0.6, CH_2Cl_2); ^1H NMR

(500 MHz, $CDCl_3$, δ_H) 7.53-7.50 (m, 2 H, Ar), 7.40-7.26 (m, 12 H, Ar), 4.70 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.68 (s, 1 H, H-1), 4.64 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.58 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.54 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.53 (dd, 1 H, J = 6.8, 0.7 Hz, H-4), 4.05 (d, 1 H, J = 2.8 Hz, H-2), 3.92 (dd, 1 H, J = 2.8, 0.7 Hz, H-3), 3.77 (ddd, 1 H, J = 6.8, 5.0, 4.0 Hz, H-5), 3.71 (dd, 1 H, J = 10.8, 4.0 Hz, H-6), 3.69 (dd, 1 H, J = 10.8, 5.0 Hz, H-6), 2.42 (s, 3 H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 141.98 (Ar), 138.39 (Ar), 137.94 (Ar), 137.16 (Ar), 130.06 (Ar × 2), 128.44 (Ar × 2), 128.28 (Ar × 2), 127.77 (Ar × 2), 127.75 (Ar), 127.72 (Ar × 2), 127.60 (Ar), 124.61 (Ar × 2), 96.25 (C-1), 81.48 (C-4), 77.96 (C-5), 73.57 ($PhCH_2$), 73.08 ($PhCH_2$), 70.24 (C-6), 55.98 (C-3), 55.14 (C-2), 21.43 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{27}H_{28}O_5SNa$ 487.1550, found 487.1550. **4b**: R_f 0.18 (2:1, hexanes: EtOAc); $[\alpha]_D$ -176.8 (*c* 0.16, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.56 (d, 2 H, J = 8.2 Hz, Ar), 7.36-7.26 (m, 12 H, Ar), 4.82 (s, 1 H, H-1), 4.66 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.60 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.55 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.50 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.41 (dd, 1 H, J = 6.8, 0.8 Hz, H-4), 4.12 (d, 1 H, J = 2.8 Hz, H-2), 3.81 (dd, 1 H, J = 2.8, 0.8 Hz, H-3), 3.72-3.69 (m, 1 H, H-5), 3.66-3.61 (m, 2 H, H-6 × 2), 2.41 (s, 3 H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 142.30 (Ar), 138.47 (Ar), 136.47 (Ar), 129.92 (Ar), 128.38 (Ar × 2), 128.22 (Ar × 2), 127.76 (Ar × 2), 127.72 (Ar × 2), 127.66 (Ar), 127.64 (Ar × 2), 127.51(Ar), 125.38 (Ar × 2), 94.61 (C-1), 82.56 (C-4), 78.04 (C-5), 73.48 ($PhCH_2$), 72.96 ($PhCH_2$), 70.37 (C-6), 56.36 (C-3), 56.00 (C-2), 21.53 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{27}H_{28}O_5S$ 487.1550, found 487.1551.

_p_-Tolyl 2,3-anhydro-5,6-di-_O_-benzoyl-1-thio-β-D-gulofuranoside (5).



Benzoyl chloride (850 μL, 7.5 mmol) was added dropwise to a solution of **14** (800 mg, 3.0 mmol) in pyridine (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solution was diluted with CH_2Cl_2 (50 mL), washed with with sat. aq. $NaHCO_3$ soln (3 × 40 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated, and purified by chromatography (6:1, hexanes:EtOAc) to yield **5** (1.28 g, 90%) as a white semi-solid foam. R_f 0.48 (3:1, hexanes:EtOAc); $[\alpha]_D$ -90.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.10-8.07 (m, 2 H, Ar), 8.03-8.00 (m, 2 H, Ar), 7.56-7.40 (m, 8 H, Ar), 7.12-7.09 (m, 2 H, Ar), 5.78 (dd, 1 H, J = 5.4, 5.0 Hz, H-5), 5.52 (s, 1 H, H-1), 4.73 (d, 2 H, J = 5.4 Hz, H-6 × 2), 4.33 (dd, 1 H, J = 5.0, 0.6 Hz, H-4), 3.90 (dd, 1 H, J = 2.8, 0.6 Hz, H-3), 3.89 (d, 1 H, J = 2.8 Hz, H-2), 2.32 (s, 3 H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.12 (C=O), 165.86 (C=O), 138.43 (Ar × 2), 133.44 (Ar × 2), 133.26 (Ar), 133.16 (Ar), 129.90 (Ar × 2), 129.88 (Ar × 2), 129.76 (Ar), 129.71 (Ar × 2), 128.57 (Ar), 128.48 (Ar × 2), 128.44 (Ar × 2), 87.07 (C-1), 74.83 (C-4), 70.81 (C-5), 63.35 (C-6), 56.96 (C-2), 54.96 (C-3), 21.14 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{27}H_{24}O_6SNa$ 499.1186, found 499.1188.

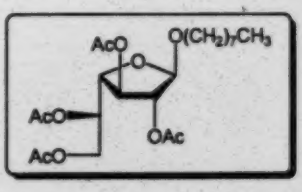
2,3-anhydro-5,6-di-_O_-benzoyl-β-D-gulofuranosyl-_p_-tolyl(R/S)-sulfoxide (6a/6b).

To a solution of **5** (360 mg, 0.75 mmol) in CH_2Cl_2 (20 mL) at –78 °C was added *m*-CPBA (160 mg, 0.68 mmol). After stirring for 2 h, the reaction mixture was warmed to

room temperature and stirred for 30 min. The solution was washed with a sat. aq. solution of $NaHCO_3$ (3 × 15 mL) and then water (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to yield a crude oil that was purified by chromatography (2:1, hexanes:EtOAc) to provide the diastereomers **6a** (200 mg, 54%) and **6b** (120 mg, 32%) as white semi-solids. **6a**: R_f 0.18 (2:1, hexanes:EtOAc); $[\alpha]_D$ +185.2 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.08-8.05 (m, 2 H, Ar), 8.03-8.00 (m, 2 H, Ar), 7.60-7.54 (m, 2 H, Ar), 7.50 (d, 2 H, J = 8.2 Hz, Ar), 7.47-7.40 (m, 4 H, Ar), 7.34 (d, 2 H, J = 8.2 Hz, Ar), 5.72 (ddd, 1 H, J = 5.9, 5.9, 4.3 Hz, H-5), 4.78-4.67 (m, 4 H, H-1, H-4, H-6 × 2), 4.08 (d, 1 H, J = 2.9 Hz, H-3), 3.98 (d, 1 H, J = 2.9 Hz, H-2), 2.40 (s, 3 H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.04 (C=O), 165.71 (C=O), 142.16 (Ar), 136.37 (Ar), 133.32 (Ar), 133.26 (Ar), 130.23 (Ar × 2), 129.87 (Ar × 2), 129.71 (Ar × 2), 129.59 (Ar), 129.52 (Ar), 128.47 (Ar × 2), 128.44 (Ar × 2), 124.12 (Ar × 2), 95.90 (C-1), 78.64 (C-4), 70.95 (C-5), 63.10 (C-6), 55.63 (C-3), 54.87 (C-2), 21.43 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{27}H_{24}O_7SNa$ 515.1135, found 515.1136. **6b**: R_f 0.09 (2:1, hexanes:EtOAc); $[\alpha]_D$ -194.9 (*c* 0.47, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.05-7.98 (m, 4 H, Ar), 7.60-7.50 (m, 4 H, Ar), 7.46-7.40 (m, 4 H, Ar), 7.27-7.23 (m, 2 H, Ar), 5.63 (ddd, 1 H, J = 5.8, 5.8, 4.8 Hz, H-5), 4.80 (s, 1 H, H-1), 4.69 (dd, 1 H, J = 5.6, 0.8 Hz, H-4), 4.67-4.60 (m, 2 H, H-6 × 2), 4.22 (d, 1 H, J = 2.8 Hz, H-2), 4.03 (dd, 1 H, J = 2.8, 0.8 Hz, H-3), 2.35 (s, 3 H, tolyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.01 (C=O), 165.68 (C=O), 142.46 (Ar × 2), 136.24 (Ar), 133.24 (Ar × 2), 129.91 (Ar × 2), 129.83 (Ar × 2), 129.70

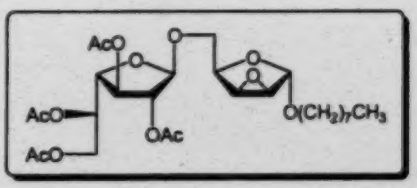
(Ar × 2), 129.54 (Ar), 128.47 (Ar × 2), 128.39 (Ar × 2), 125.21 (Ar × 2), 94.32 (C-1), 79.65 (C-4), 70.87 (C-5), 63.03 (C-6), 56.13 (C-2), 55.79 (C-3), 21.48 (tolyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{27}H_{24}O_7S$ 493.1316, found 493.1315.

***n*-Octyl 2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranoside (15).**



To a mixture of **9** (260 mg, 0.57 mmol), octanol (110 μL, 0.69 mmol) and 4 Å molecular sieves (250 mg) in CH_2Cl_2 (15 mL) was added *N*-iodosuccinimide (163 mg, 0.69 mmol) and silver triflate (44 mg, 0.17 mmol) in succession at 0 °C. After stirring for 15 min at 0 °C, the reaction mixture turned dark red, and triethylamine was added, diluted with CH_2Cl_2 (35 mL), and filtered through Celite. The filtrate was washed with a sat. aq. $Na_2S_2O_3$ soln.(3 × 30 mL), dried (Na_2SO_4), and concentrated to give a crude residue that was purified by chromatography (4:1, hexanes:EtOAc) to give **15** (105 mg, 40%) as colorless oil. R_f 0.37 (4:1, hexanes:EtOAc). The NMR spectral data for this compound matched those previously reported.[119]

***n*-Octyl 2,3-anhydro-5-*O*-(2,3,5,6-tetra-*O*-acetyl-1-β-D-galactofuranosyl)-α-D-lyxo-furanoside (16).**

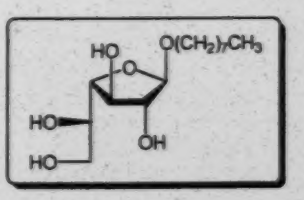


To a mixture of **9** (250 mg, 0.55 mmol), **29**[104] (134 mg, 0.55 mmol) and 4 Å molecular sieves (250 mg)

in CH_2Cl_2 (15 mL) was added *N*-iodosuccinimide (156 mg, 0.66 mmol) and silver triflate (42 mg, 0.16 mmol) in that order at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture turned dark red and was neutralized by the addition of triethylamine, then diluted with CH_2Cl_2 (35 mL) and filtered through Celite. The filtrate was washed with a sat. aq. $Na_2S_2O_3$ soln. (3 × 30 mL), dried (Na_2SO_4), and concentrated to give a crude residue that was purified by chromatography (3:1, hexanes: EtOAc) to provide **16** (281 mg, 89%) as a colorless oil. R_f 0.29 (2:1, hexanes:EtOAc); $[\alpha]_D$ -21.4 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 5.37 (ddd, 1 H, *J* = 7.0, 4.4, 3.8 Hz, H-5'), 5.10-5.08 (m, 2 H, H-1', H-2'), 5.02 (s, 1 H, H-1), 5.02-5.00 (m, 1 H, H-3'), 4.34 (dd, 1 H, *J* = 11.8, 4.4 Hz, H-6'), 4.27 (dd, 1 H, *J* = 5.9, 3.8 Hz, H-4'), 4.21 (dd, 1 H, *J* = 11.8, 7.0 Hz, H-6'), 4.19-4.16 (m, 1 H, H-4), 3.78 (dd, 1 H, *J* = 9.9, 7.3 Hz, H-5), 3.75 (dd, 1 H, *J* = 2.9, 0.7 Hz, H-3), 3.71 (ddd, 1 H, *J* = 9.5, 6.7, 6.7 Hz, octyl OCH_2), 3.65 (dd, 1 H, *J* = 9.9, 5.9 Hz, H-5), 3.65 (d, 1 H, *J* = 2.9 Hz, H-2), 3.44 (ddd, 1H dd, *J* = 9.5, 6.7, 6.7 Hz, octyl OCH_2), 2.12 (s, 3 H, acyl CH_3), 2.10 (s, 3 H, acyl CH_3), 2.07 (s, 3 H, acyl CH_3), 2.05 (s, 3 H, acyl CH_3), 1.60-1.53 (m, 2 H, octyl CH_2), 1.35-1.22 (m, 10 H, octyl CH_2), 0.87 (dd, 3 H, *J* = 7.0, 7.0 Hz, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.49 (C=O), 169.99 (C=O), 169.89 (C=O), 169.58 (C=O), 105.50 (C-1'), 101.23 (C-1), 81.31 (C-2'), 80.04 (C-4'), 76.49 (C-3'), 74.52 (C-4), 69.23 (C-5'), 68.61 (octyl OCH_2), 65.43 (C-5), 62.56 (C-6'), 56.39 (C-2), 54.39 (C-3), 31.78 (octyl CH_2), 29.61 (octyl CH_2), 29.32 (octyl CH_2), 29.22 (octyl CH_2), 26.02 (octyl CH_2), 22.62 (octyl CH_2), 20.78 (acyl CH_3), 20.73 (acyl CH_3), 20.66

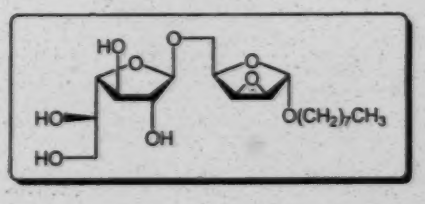
(acyl CH_3), 20.64 (acyl CH_3), 14.06 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{27}H_{42}O_{13}Na$ 597.2518, found 597.2518.

_n_-Octyl β-D-galactofuranoside (17).



To a solution of **15** (66 mg, 0.14 mmol) in CH_3OH (2 mL) and CH_2Cl_2 (2 mL) was added solid $NaOCH_3$ until the pH was ~10. The solution was allowed to stir at room temperature for 5 h, followed by neutralization with acetic acid. The resulting mixture was concentrated and the residue was purified by chromatography (10:1, CH_2Cl_2:CH_3OH), to yield the **17** (34 mg, 81%) as a colorless oil. R_f 0.37 (10:1, CH_2Cl_2:CH_3OH). The NMR spectral data for this compound matched those previously reported.[119]

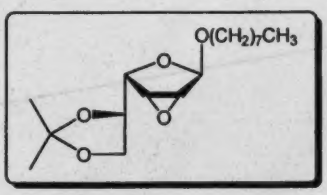
_n_-Octyl 2,3-anhydro-5-*O*-(β-D-galactofuranosyl)-α-D-lyxofuranoside (18).



To a solution of **16** (221 mg, 0.39 mmol) in CH_3OH (4 mL) and CH_2Cl_2 (4 mL) was added solid $NaOCH_3$ until the pH was ~10. The solution was stirred at room temperature for 5 h, followed by neutralization with acetic acid. The resulting mixture was concentrated and purified by chromatography (11:1, CH_2Cl_2:CH_3OH), to provide **18** (136 mg, 87%) as a colorless oil. R_f 0.38 (10:1, CH_2Cl_2:CH_3OH); $[\alpha]_D$ -28.9 (*c* 0.2, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 5.00 (s, 1 H, H-1), 4.91 (d, 1 H, J = 1.7 Hz, H-1'), 4.13 (dd, 1 H, J = 6.1, 6.0 Hz, H-4), 4.00 (dd, 1 H, J = 6.3, 3.7 Hz, H-3'), 3.97

(dd, 1 H, J = 3.7, 1.7 Hz, H-2'), 3.96 (dd, 1 H, J = 6.3, 3.1 Hz, H-4'), 3.86-3.82 (m, 2 H, H-3, H-5), 3.73-3.68 (m, 2 H, H-5', octyl OCH_2), 3.64 (d, 1 H, J = 2.9 Hz, H-2), 3.63-3.56 (m, 3 H, H-6' × 2, H-5), 3.46 (ddd, 1 H, J = 9.6, 6.6, 6.6 Hz, octyl OCH_2), 1.60-1.52 (m, 2 H, octyl CH_2), 1.34-1.22 (m, 10 H, octyl CH_2), 0.87 (dd, 3 H, J = 6.9, 6.9 Hz, octyl CH_3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 109.68 (C-1'), 102.71 (C-1), 84.68 (C-4'), 83.17 (C-2'), 78.84 (C-3'), 76.37 (C-4), 72.66 (C-5'), 69.42 (octyl OCH_2), 67.10 (C-5), 64.54 (C-6'), 57.14 (C-2), 55.33 (C-3), 32.99 (octyl CH_2), 32.56 (octyl CH_2), 30.79 (octyl CH_2), 30.47 (octyl CH_2), 30.40 (octyl CH_2), 27.20 (octyl CH_2), 14.42 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{19}H_{34}O_9Na$ 429.2095, found 429.2093.

_n_-Octyl 2,3-anhydro-5,6-_O_-isopropylidene-β-D-gulofuranoside (19).

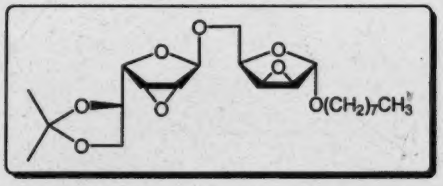


To a solution of **17** (29 mg, 0.10 mmol) and 2,2-dimethoxypropane (0.10 mL, 0.80 mmol) in acetone (1.0 mL) was added *p*-toluenesufonic acid (0.2 mg, cat.) at room temperature. The solution was stirred for 3 h and neutralized with triethylamine. TLC showed a spot at R_f 0.55 (15:1, CH_2Cl_2: CH_3OH). The mixture was concentrated and the resulting oil was dissolved in THF (1.0 mL), followed by the addition of PPh_3 (31 mg, 0.12 mmol). DIAD (23 μL, 0.12 mmol) was then added dropwise at 0 °C. The reaction mixture was warmed to room temperature over 30 min. The resulting mixture was concentrated and the residue was purified by chromatography (8:1, hexanes:EtOAc) to yield **19** (15 mg, 49% over two steps) as a white foam. R_f 0.58 (4:1, hexanes:EtOAc);

$[\alpha]_D$ -29.1 (*c* 0.4, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 5.08 (s, 1 H, H-1), 4.30 (ddd, 1 H, *J* = 7.1, 6.6, 6.5 Hz, H-5), 4.12 (dd, 1 H, *J* = 8.3, 6.5 Hz, H-6), 4.04 (d, 1 H, *J* = 7.1 Hz, H-4), 3.94 (dd, 1 H, *J* = 8.3, 6.6 Hz, H-6), 3.79 (ddd, 1 H, *J* = 9.5, 6.7, 6.7 Hz, octyl OCH_2), 3.64 (d, 1 H, *J* = 2.9 Hz, H-2), 3.61 (d, 1 H, *J* = 2.9 Hz, H-3), 3.46 (ddd, 1 H, *J* = 9.5, 6.7, 6.7 Hz, octyl OCH_2), 1.61-1.54 (dd, 2 H, octyl CH_2), 1.47 (s, 3 H, isopropylidene CH_3), 1.38 (s, 3 H, isopropylidene CH_3), 1.36-1.24 (m, 10 H, octyl CH_2), 0.99-0.86 (m, 3 H, *J* = 7.0, 7.0 Hz octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 109.83 (isopropylidene C), 101.29 (C-1), 77.13 (C-4), 75.24 (C-5), 68.71 (octyl OCH_2), 65.73 (C-6), 55.65 (C-2), 53.50 (C-3), 31.80 (octyl CH_2), 29.61 (octyl CH_2), 29.32 (octyl CH_2), 29.23 (octyl CH_2), 26.68 (isopropylidene CH_3), 26.01 (octyl CH_2), 25.22 (isopropylidene CH_3), 22.64 (octyl CH_2), 14.08 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{17}H_{30}O_5Na$ 337.1986, found 337.1984.

_n_-Octyl 2,3-anhydro-5-*O*-(2,3-anhydro-5,6-*O*-isopropylidene-β-D-gulofuranosyl)-α-D-lyxofuranoside (20)

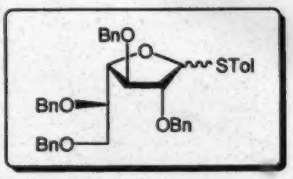
To a solution of **18** (106 mg, 0.26 mmol) and 2,2-dimethoxypropane (0.26 mL, 2.1 mmol) in acetone (2.0 mL) was added *p*-toluenesufonic acid



(0.5 mg, cat.) at room temperature. The solution was stirred for 3 h, and neutralized with triethylamine. TLC showed a spot at R_f 0.58 (10:1, CH_2Cl_2:CH_3OH). The mixture was concentrated and the resulting oil was dissolved in THF (2.0 mL), followed by the

addition of PPh_3 (82 mg, 0.31 mmol). DIAD (61 μL, 0.31 mmol) was then added dropwise at 0 °C. The reaction mixture was warmed to room temperature over 30 min, and stirred for another 40 min. The resulting mixture was concentrated and the residue was purified by chromatography (4:1, hexanes:EtOAc) to yield **20** (83 mg, 74% over two steps) as a white foam. R_f 0.27 (4:1, hexanes:EtOAc); $[\alpha]_D$ -4.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 5.16 (s, 1 H, H-1'), 5.05 (s, 1 H, H-1), 4.29 (ddd, 1 H, *J* = 6.8, 6.6, 6.5 Hz, H-5'), 4.19-4.15 (m, 1 H, H-4), 4.10 (dd, 1 H, *J* = 8.5, 6.5 Hz, H-6'), 4.07 (d, 1 H, *J* = 6.8 Hz, H-4'), 3.97 (dd, 1 H, *J* = 10.5, 5.3 Hz, H-5), 3.94 (dd, 1 H, *J* = 8.5, 6.6 Hz, H-6'), 3.73 (ddd, 1 H, *J* = 9.6, 6.7, 6.7 Hz, octyl OCH_2), 3.72-3.68 (m, 3 H, H-2, H-3', H-5), 3.64-3.62 (m, 2 H, H-2', H-3), 3.45 (ddd, 1H, *J* = 9.6, 6.7, 6.7 Hz, octyl OCH_2), 1.60-1.53 (m, 2 H, octyl CH_2), 1.47 (s, 3 H, isopropylidene CH_3), 1.38 (s, 3 H, isopropylidene CH_3), 1.36-1.23 (m, 10 H, octyl CH_2), 0.90-0.88 (m, 3 H, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 109.84 (isopropylidene C), 101.84 (C-1'), 101.32 (C-1), 77.32 (C-4'), 75.19 (C-5'), 75.11 (C-4), 68.64 (C-5), 67.31 (octyl OCH_2), 65.67 (C-6'), 56.01 (C-2'), 55.58 (C-2), 54.18 (C-3'), 53.40 (C-3), 31.79 (octyl CH_2), 29.61 (octyl CH_2), 29.32 (octyl CH_2), 29.22 (octyl CH_2), 26.66 (isopropylidene CH_3), 26.01 (octyl CH_2), 25.19 (isopropylidene CH_3), 22.62 (octyl CH_2), 14.07 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{22}H_{36}O_8Na$ 451.2302, found 451.2307.

***p*-Tolyl 2,3,5,6-tetra-*O*-benzyl-1-thio-α/β-D-galactofuranoside (21).**



To a solution of an anomeric mixture of **10** and **11** (643 mg, 2.22 mmol) in DMF (15 mL) at 0 °C was added NaH (0.585 g, 14.6 mmol, 60% dispersion in oil) and the solution was stirred for 10 min. Benzyl bromide (1.3 mL, 11.1 mmol) was added dropwise and the solution was stirred for 5 h at room temperature. The reaction mixture was quenched by adding a few drops of CH_3OH, diluted with CH_2Cl_2 (50 mL), and washed with a sat. aq. $NaHCO_3$ soln. (3 × 40 mL) and water (3 × 40 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated, and the resulting residue was purified by chromatography (7:1, hexanes:EtOAc) to provide **21** (1.402 g, 98%) as a colorless oil. R_f 0.50 (6:1, hexanes: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.51-7.47 (m, 1 H, Ar), 7.43-7.23 (m, 21 H, Ar), 7.13-7.09 (m, 2 H, Ar), 5.67 (d, 0.4 H, J = 4.7 Hz, H-1α), 5.59 (d, 0.6 H, J = 2.8 Hz, H-1β), 4.81 (d, 0.4 H, J = 11.8 Hz, $PhCH_2$α), 4.77-4.66 (m, 1.8 H, $PhCH_2$), 4.59-4.46 (m, 5.2 H, $PhCH_2$), 4.39 (dd, 0.6 H, J = 7.1, 3.4 Hz, H-4β), 4.36 (d, 0.6 H, J = 11.7 Hz, $PhCH_2$β), 4.30-4.26 (m, 0.8 H, H-2α, H-3α), 4.17-4.10 (m, 1.6 H, H-4α, H-3β, H-2β), 4.40 (ddd, 0.4 H, J = 6.5, 6.5, 4.6 Hz, H-5α), 3.86 (ddd, 0.6 H, J = 5.9, 5.9, 3.4 Hz, H-5β), 3.78-3.69 (m, 1.6 H, H-6β × 2, H-6α), 3.61 (dd, 0.4 H, J = 10.5, 6.5 Hz, H-6α), 2.35 (s, 1.8 H, tolyl CH_3β), 2.34 (s, 1.2 H, tolyl CH_3α); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.94 (Arα), 138.43 (Arβ), 138.33 (Arα), 138.31 (Arβ), 137.84 (Arα), 137.79 (Arβ), 137.52 (Arα), 137.44 (Arβ), 137.31 (Arα), 136.79 (Arβ), 132.08 (Arβ), 131.84 (Arα), 131.34 (Arα), 130.91 (Arβ), 129.64 (Arα), 129.62 (Arβ), 128.48-127.36 (Ar), 90.29 (C-1β),

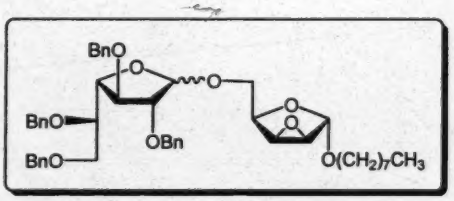
89.96 (C-1α), 88.60 (C-2β), 84.38 (C-2α), 84.07 (C-4α), 82.94 (C-3β), 82.02 (C-3α), 80.60 (C-4β), 78.61 (C-5α), 76.33 (C-5β), 73.51 ($PhCH_2$β), 73.40 ($PhCH_2$α), 73.36 ($PhCH_2$α), 73.30 ($PhCH_2$β), 72.44 ($PhCH_2$α), 72.20 ($PhCH_2$β), 72.04 ($PhCH_2$β), 71.87 ($PhCH_2$α), 70.78 (C-6αβ), 68.02 21.14 (tolyl CH_3β), 21.09 (tolyl CH_3α). HRMS (ESI) calcd. for (M+Na) $C_{41}H_{42}O_5SNa$ 669.2645, found 669.2642.

***n*-Octyl 2,3,5,6-tetra-*O*-benzyl-α/β-D-galactofuranoside (22a/22b).**

To a mixture of **21** (490 mg, 0.76 mmol), octanol (0.14 mL, 0.91 mmol) and 4 Å molecular sieves (0.5 g) in CH_2Cl_2 (20 mL) was added *N*-iodosuccinimide (216 mg, 0.91 mmol) at 0 °C. After stirring for 10 min at 0 °C, the reaction mixture was neutralized with triethylamine. The resulting solution was then diluted with CH_2Cl_2 (30 mL) and filtered through Celite. The filtrate was washed with a sat. aq. $Na_2S_2O_3$ soln. (3 × 30 mL), dried (Na_2SO_4), and concentrated to give a crude residue that was purified by chromatography (10:1, hexanes:EtOAc) to give **22a** (82 mg, 17%) and **22b** (307 mg, 62%) as colorless oils. **22a**: R_f 0.47 (6:1, hexanes:EtOAc). **20b**: R_f 0.37 (6:1, hexanes:EtOAc); $[\alpha]_D$ +27.7 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.41-7.20 (m, 20 H, Ar), 4.90 (d, 1 H, J = 4.3 Hz, H-1), 4.76 (d, 2 H, J = 12.2 Hz, $PhCH_2$), 4.66 (d, 2 H, J = 11.6 Hz, $PhCH_2$), 4.58 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.52 (d, 2 H, J = 11.8 Hz, $PhCH_2$), 4.48 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.31 (dd, 1 H, J = 7.5, 7.0 Hz, H-3), 4.07 (dd, 1 H, J = 7.5, 4.3 Hz, H-2), 3.99 (dd, 1 H, J = 7.0, 6.6 Hz, H-4), 3.75-3.65 (m, 3 H, H-5, H-6, octyl OCH_2), 3.60 (dd,

1 H, J = 10.4, 6.3 Hz, H-6) 3.33 (ddd, 1 H, J = 9.6, 7.0, 7.0 Hz, octyl OCH_2), 1.64-1.52 (m, 2 H, octyl CH_2), 1.36-1.24 (m, 10 H, octyl CH_2), 0.91 (dd, 3 H, J = 7.0, 7.0 Hz, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.93 (Ar), 138.33 (Ar × 2), 137.80 (Ar), 128.41 (Ar × 2), 128.32 (Ar × 2), 128.31 (Ar × 2), 128.18 (Ar × 2), 128.15 (Ar × 2), 127.91 (Ar), 127.85 (Ar × 2), 127.80 (Ar × 2), 127.60 (Ar), 127.55 (Ar × 2), 127.51 (Ar), 127.35 (Ar), 99.99 (C-1), 84.26 (C-2), 81.26 (C-3), 80.42 (C-4), 79.92 (C-5), 73.36 ($PhCH_2$), 73.09 ($PhCH_2$), 72.35 ($PhCH_2$), 72.27 ($PhCH_2$), 70.50 (C-6), 68.02 (octyl OCH_2), 31.88 (octyl CH_2), 29.54 (octyl CH_2), 29.50 (octyl CH_2), 29.32 (octyl CH_2), 26.29 (octyl CH_2), 22.69 (octyl CH_2), 14.12 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{42}H_{52}O_6Na$ 675.3656, found 675.3657.

_n_-Octyl 2,3-anhydro-5-_O_-(2,3,5,6-tetra-_O_-benzyl-α/β-D-galactofuranosyl)-α-D-lyxo-furanoside (23).

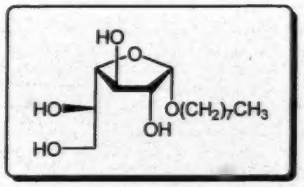


To a mixture of **21** (490 mg, 0.76 mmol), **29** (186 μL, 0.76 mmol) and 4 Å molecular sieves (0.5 g) in CH_2Cl_2 (20 mL) was added *N*-iodosuccinimide (216 mg, 0.91 mmol) and silver triflate (59 mg, 0.23 mmol) in order at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was neutralized with triethylamine, diluted with CH_2Cl_2 (30 mL) and then filtered through Celite. The filtrate was washed with a sat. aq. $Na_2S_2O_3$ soln. (3 × 30 mL), dried (Na_2SO_4), and concentrated to give a crude residue that was purified by chromatography (6:1, hexanes:EtOAc) to give an α/β

mixture of **23** (405 mg, 70%) as a colorless oil. R_f 0.27 (6:1, hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.42-7.25 (m, 20 H, Ar), 5.03 (s, 1 H, H-1), 4.94 (d, 1 H, J = 4.4 Hz, H-1'), 4.82-4.49 (m, 8 H, $PhCH_2$), 4.39 (dd, 1 H, J = 7.7, 7.3 Hz, H-3'), 4.17 (dd, 1 H, J = 8.4, 5.0 Hz, H-4), 4.11 (dd, 1 H, J = 7.7, 4.4 Hz, H-2'), 4.03 (dd, 1 H, J = 7.3, 4.9 Hz, H-4'), 3.88 (dd, 1 H, J = 9.8, 5.0 Hz, H-5), 3.77-3.66 (m, 4 H, H-5', H-6' ×2, octyl OCH_2), 3.75 (d, 1 H, J = 2.8 Hz, H-3), 3.63 (d, 1 H, J = 2.8 Hz, H-2), 3.55 (dd, 1 H, J = 9.8, 8.4 Hz, H-5), 3.45 (ddd, 1 H, J = 9.4, 6.7, 6.7 Hz, octyl OCH_2), 1.64-1.58 (m, 2 H, octyl CH_2), 1.39-1.27 (m, 10 H, octyl CH_2), 0.95-0.91 (dd, 3 H, J = 7.0, 7.0 Hz, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.71 (Ar), 138.31 (Ar), 138.28 (Ar), 137.75 (Ar), 128.66 (Ar), 128.42 (Ar), 128.30 (Ar), 128.12 (Ar), 128.99 (Ar), 127.93 (Ar), 127.75 (Ar), 127.59 (Ar), 127.49 (Ar), 101.12 (C-1), 100.42 (C-1'), 84.25 (C-2'), 80.33 (C-3'), 80.31 (C-4'), 78.57 (C-5'), 74.53 (C-4), 73.45 ($PhCH_2$), 73.23 ($PhCH_2$), 72.48 ($PhCH_2$), 72.35 ($PhCH_2$), 70.52 (C-6'). 68.48 (octyl OCH_2), 65.95 (C-5), 56.74 (C-2), 54.66 (C-3), 31.86 (octyl CH_2), 29.70 (octyl CH_2), 29.43 (octyl CH_2), 29.29 (octyl CH_2), 26.11 (octyl CH_2), 22.70 (octyl CH_2), 14.16 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{47}H_{58}O_9Na$ 789.3973, found 789.3973. (NMR data only for α-anomer)

***n*-Octyl α-D-galactofuranoside (24).**

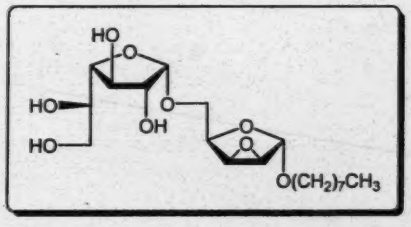
To a solution of **22b** (201 mg, 0.31 mmol) in methanol (2.0 mL) was added 20% palladium hydroxide on carbon and the



reaction was stirred under positive pressure of hydrogen for 12 h. The resulting mixture was filtered through Celite and concentrated to give a crude residue that was purified by chromatography (11:1, CH_2Cl_2:CH_3OH) to yield **24** (76 mg, 85%) as a white foam. R_f 0.36 (10:1, CH_2Cl_2:CH_3OH); $[\alpha]_D$ +83.5 (*c* 0.2, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 4.83 (d, 1 H, J = 4.6 Hz, H-1), 4.07 (dd, 1 H, J = 7.8, 7.0 Hz, H-3), 3.93 (dd, 1 H, J = 7.8, 4.6 Hz, H-2), 3.78 (ddd, 1 H, J = 9.6, 6.7, 6.7 Hz, octyl OCH_2), 3.71 (dd, 1 H, J = 7.0, 5.2 Hz, H-4), 3.64-3.59 (m, 2 H, H-5, H-6), 3.57-3.51 (m, 1 H, H-6), 3.45 (ddd, 1 H, J = 9.6, 6.7, 6.7 Hz, octyl OCH_2), 1.64-1.57 (m, 2 H, octyl CH_2), 1.40-1.24 (m, 10 H, octyl CH_2), 0.91-0.86 (m, 3 H, octyl CH_3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 102.87 (C-1), 83.58 (C-4), 78.94 (C-2), 76.41 (C-3), 74.48 (C-5), 69.75 (octyl OCH_2), 64.21 (C-6), 33.02 (octyl CH_2), 30.75 (octyl CH_2), 30.60 (octyl CH_2), 30.42 (octyl CH_2), 27.22 (octyl CH_2), 23.73 (octyl CH_2), 14.43 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{14}H_{28}O_6Na$ 315.1778, found 315.1778.

***n*-Octyl 2,3-anhydro-5-*O*-(α-D-galactofuranosyl)-α-D-lyxofuranoside (25).**

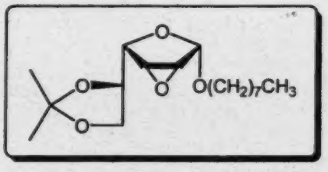
To a solution of **23** (140 mg, 0.18 mmol) in methanol (2.0 mL) was added 20% palladium hydroxide on carbon and the reaction was stirred under positive pressure of hydrogen for 12 h. The resulting mixture was filtered through Celite and concentrated to give a crude residue that was purified by chromatography (11:1, CH_2Cl_2:CH_3OH) to yield **25** (61 mg, 82%) as a



colorless oil. R_f 0.38 (10:1, CH_2Cl_2:CH_3OH); $[\alpha]_D$ +98.7 (*c* 0.2, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 5.02 (s, 1 H, H-1), 4.87 (d, 1 H, *J* = 4.7 Hz, H-1'), 4.19 (dd, 1 H, *J* = 6.5, 5.9 Hz, H-4), 4.16 (dd, 1 H, *J* = 8.1, 7.3 Hz, H-3'), 3.95 (dd, 1 H, *J* = 8.1, 4.7 Hz, H-2'), 3.88 (d, 1 H, *J* = 2.9 Hz, H-3), 3.86 (dd, 1 H, *J* = 10.1, 6.5 Hz, H-5), 3.75 (dd, 1 H, *J* = 7.3, 4.0 Hz, H-4'), 3.74-3.68 (m, 2 H, H-5, octyl OCH_2), 3.65 (d, 1 H, *J* = 2.9 Hz, H-2), 3.64-3.54 (m, 3 H, H-6' × 2, H-5'), 3.46 (ddd, 1 H, *J* = 9.5, 6.6, 6.6 Hz, octyl OCH_2), 1.61-1.52 (m, 2 H, octyl CH_2), 1.34-1.23 (m, 10 H, octyl CH_2), 0.91-0.83 (m, 3 H, *J* = 7.0, 7.0 Hz, octyl CH_3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 103.17 (C-1'), 102.69 (C-1), 83.40 (C-4'), 78.87 (C-2'), 76.27 (C-4), 75.74 (C-3'), 73.57 (C-5'), 69.53 (octyl OCH_2), 68.27 (C-5), 64.30 (C-6'), 57.16 (C-2), 55.24 (C-3), 33.00 (octyl CH_2), 30.79 (octyl CH_2), 30.51 (octyl CH_2), 30.41 (octyl CH_2), 27.21 (octyl CH_2), 23.72 (octyl CH_2), 14.43 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{19}H_{34}O_9Na$ 429.2095, found 429.2094.

_n_-Octyl 2,3-anhydro-5,6-*O*-isopropylidene-β-D-gulofuranoside (26).

To a solution of **24** (61 mg, 0.21 mmol) and 2,2-dimethoxypropane (0.21 mL, 1.7 mmol) in acetone (1.5 mL) was added *p*-toluenesufonic acid (0.4 mg, cat.) at room temperature. The solution was stirred for 4 h, and neutralized with triethylamine. The mixture was concentrated and the resulting oil was dissolved in THF (2.0 mL), followed by the addition of PPh_3 (67 mg, 0.25 mmol). DIAD (51 μL, 0.25 mmol) was then added

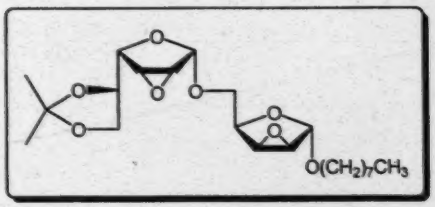


dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min. The resulting mixture was concentrated and the residue was purified by chromatography (4:1, hexanes:EtOAc) to yield **26** (43 mg, 65% over two steps) as a white foam. R_f 0.26 (4:1, hexanes:EtOAc); $[\alpha]_D$ +44.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 5.08 (s, 1 H, H-1), 4.15 (ddd, 1 H, J = 6.7, 6.6, 6.6 Hz, H-5), 4.11 (dd, 1 H, J = 8.5, 6.6 Hz, H-6), 3.98 (dd, 1 H, J = 8.5, 6.7 Hz, H-6), 3.88 (dd, 1 H, J = 6.6, 0.7 Hz, H-4), 3.82 (ddd, 1 H, J = 9.6, 6.8, 6.8 Hz, octyl OCH_2), 3.66 (d, 1 H, J = 3.0 Hz, H-2), 3.58 (dd, 1 H, J = 3.0, 0.7 Hz, H-3), 3.55 (ddd, 1 H, J = 9.6, 6.8, 6.8 Hz, octyl OCH_2), 1.64-1.58 (m, 2 H, octyl CH_2), 1.46 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3), 1.35-1.22 (m, 10 H, octyl CH_2), 0.89-0.84 (dd, 3 H, J = 7.0, 7.0 Hz, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 109.71 (isopropylidene C), 101.61 (C-1), 77.30 (C-4), 75.44 (C-5), 69.85 (octyl OCH_2), 65.43 (C-6), 54.87 (C-2), 53.87 (C-3), 31.78 (octyl CH_2), 29.67 (octyl CH_2), 29.34 (octyl CH_2), 29.21 (octyl CH_2), 26.62 (isopropylidene CH_3), 25.90 (octyl CH_2), 25.17 (isopropylidene CH_3), 22.62 (octyl CH_2), 14.06 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{17}H_{30}O_5Na$ 337.1986, found 337.1984.

_n_-Octyl 2,3-anhydro-5-_O_-(2,3-anhydro-5,6-_O_-isopropylidene-1-β-D-gulofuranosyl)-α-D-lyxofuranoside (27).

To a solution of **25** (44 mg, 0.11 mmol) and 2,2-dimethoxypropane (0.11 mL, 0.87 mmol) in acetone (1.0 mL) was added *p*-toluenesufonic acid (0.2 mg, cat.) at room temperature.

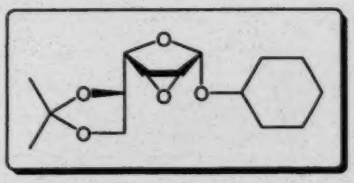
The solution was stirred for 4 h, and neutralized with triethylamine. The mixture was concentrated and the resulting oil was dissolved in THF (1.0



mL), followed by the addition of PPh_3 (34 mg, 0.13 mmol). DIAD (25 μL, 0.13 mmol) was then added dropwise at 0 °C. The reaction mixture was warmed to room temperature and kept strirring for 40 min. The resulting mixture was concentrated and the residue was purified by chromatography (4:1, hexanes:EtOAc) to yield **27** (18 mg, 39% over two steps) as a white foam. R_f 0.22 (2:1, hexanes:EtOAc); $[\alpha]_D$ +38.3 (*c* 2.3, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 5.18 (s, 1 H, H-1'), 5.02 (s, 1 H, H-1), 4.35 (ddd, 1 H, *J* = 7.3, 6.7, 6.6 Hz, H-5'), 4.21 (dd, 1 H, *J* = 7.0, 5.7 Hz, H-4), 4.12 (dd, 1 H, *J* = 8.3, 7.3 Hz, H-6'), 4.00-3.94 (m, 2 H, H-6', H-5), 3.91 (d, 1 H, *J* = 6.7 Hz, H-4'), 3.84-3.78 (m, 1 H, H-5), 3.79 (d, 1 H, *J* = 2.8 Hz, H-2), 3.74-3.68 (m, 1 H, octyl OCH_2), 3.71 (d, 1 H, *J* = 2.9 Hz, H-2'), 3.64 (d, 1 H, *J* = 2.8 Hz, H-3), 3.60 (d, 1 H, *J* = 2.9 Hz, H-3'), 3.43 (ddd, 1H, *J* = 9.3, 6.9, 6.9 Hz, octyl OCH_2), 1.59-1.52 (m, 2 H, octyl CH_2), 1.46 (s, 3 H, isopropylidene CH_3), 1.38 (s, 3 H, isopropylidene CH_3), 1.34-1.21 (m, 10 H, octyl CH_2), 0.89-0.85 (m, 3 H, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 109.82 (isopropylidene C), 101.57 (C-1'), 101.12 (C-1), 77.36 (C-4'), 75.29 (C-5'), 74.66 (C-4), 68.53 (octyl OCH_2), 66.89 (C-5), 65.40 (C-6'), 56.43 (C-3), 54.71 (C-2'), 54.36 (C-2), 53.87 (C-3'), 31.79 (octyl CH_2), 29.61 (octyl CH_2), 29.32 (octyl CH_2), 29.21 (octyl CH_2), 26.63 (isopropylidene CH_3), 26.02 (octyl CH_2), 25.17 (isopropylidene CH_3), 22.62 (octyl CH_2),

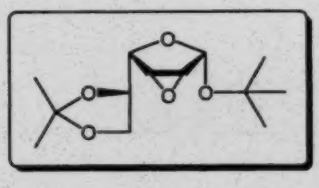
14.07 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{22}H_{36}O_8Na$ 451.2302, found 451.2308.

Cyclohexyl 2,3-anhydro-5,6-*O*-isopropylidene-α-D-gulofuranoside (36).



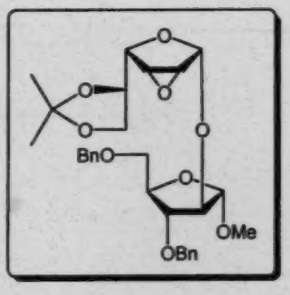
The glycosylation was carried out following the general protocol, and **36** was isolated by chromatography (4:1, hexanes:EtOAc) as a white foam. R_f 0.25 (4:1, hexanes: EtOAc); $[\alpha]_D$ +61.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 5.19 (d, 1 H, J = 0.6 Hz, H-1), 4.36 (ddd, 1 H, J = 6.6, 6.6, 6.5 Hz, H-5), 4.11 (dd, 1 H, J = 8.5, 6.6 Hz, H-6), 4.00 (dd, 1 H, J = 8.5, 6.6 Hz, H-6), 3.87 (dd, 1 H, J = 6.5, 0.8 Hz, H-4), 3.67-3.61 (m, 1 H, cyclohexyl OCH), 3.64 (dd, 1 H, J = 3.0, 0.6 Hz, H-2), 3.58 (dd, 1 H, J = 3.0, 0.8 Hz, H-3), 2.01-1.89 (m, 2 H, cyclohexyl CH_2), 1.77-1.71 (m, 2 H, cyclohexyl CH_2), 1.56-1.50 (m, 1 H, cyclohexyl CH_2), 1.46 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3), 1.46-1.13 (m, 5 H, cyclohexyl CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 109.72 (isopropylidene C), 100.04 (C-1), 77.65 (cyclohexyl OCH), 77.25 (C-4), 75.55 (C-5), 65.48 (C-6), 55.39 (C-2), 53.84 (C-3), 33.42 (cyclohexyl CH_2), 32.31 (cyclohexyl CH_2), 26.63 (isopropylidene CH_3), 25.53 (cyclohexyl CH_2 × 2), 25.22 (isopropylidene CH_3), 24.20 (cyclohexyl CH_2). HRMS (ESI) calcd. for (M+Na) $C_{15}H_{24}O_5Na$ 307.1516, found 307.1516.

***tert*-Butyl 2,3-anhydro-5,6-*O*-isopropylidene-α-D-gulofuranoside (37).**



The glycosylation was carried out following the general protocol, and **37** was isolated by chromatography (4:1, hexanes:EtOAc) as a white foam. R_f 0.21 (4:1, hexanes: EtOAc); $[\alpha]_D$ +67.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 5.24 (s, 1 H, H-1), 4.37 (ddd, 1 H, J = 6.8, 6.5, 6.0 Hz, H-5), 4.10 (dd, 1 H, J = 8.5, 6.5 Hz, H-6), 4.05 (dd, 1 H, J = 8.5, 6.8 Hz, H-6), 3.87 (d, 1 H, J = 6.0 Hz, H-4), 3.59-3.58 (m, 2 H, H-2, H-3), 1.47 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3), 1.29 (s, 9 H, *t*-butyl CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 109.54 (isopropylidene C), 96.45 (C-1), 77.00 (C-4), 75.63 (*t*-butyl $\underline{C}(CH_3)$), 75.51 (C-5), 65.54 (C-6), 56.04 (C-2), 53.49 (C-3), 28.55 (*t*-butyl CH_3 × 3), 26.62 (isopropylidene CH_3), 25.22 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{13}H_{22}O_5Na$ 281.1359, found 281.1357.

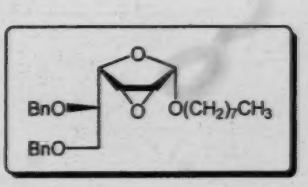
Methyl 3,5-di-*O*-benzyl-2-*O*-(2,3-anhydro-5,6-*O*-isopropylidene-α-D-gulofuranosyl)-α-D-arabinofuranoside (38).



The glycosylation was carried out following the general protocol, and **38** was isolated by chromatography (1:1, hexanes: EtOAc) as a colorless syrup. R_f 0.44 (1:1, hexanes:EtOAc); $[\alpha]_D$ +77.5 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.35-7.27 (m, 10 H, Ar), 5.02 (s, 1 H, H-1), 4.98 (d, 1 H, J = 0.5 Hz, H-1'), 4.64-4.54 (m, 4 H, $PhCH_2$), 4.34 (ddd, 1 H, J = 6.5, 6.5, 6.5 Hz, H-5'), 4.25 (d, 1 H, J = 2.9 Hz, H-2),

4.20-4.17 (m, 1 H, H-4), 4.08 (dd, 1 H, J = 8.5, 6.5 Hz, H-6'), 4.01 (dd, 1 H, J = 8.5, 6.5 Hz, H-6'), 3.93-3.90 (m, 2 H, H-4', H-3), 3.67-3.60 (m, 3 H, H-5 × 2, H-3'), 3.54 (dd, 1 H, J = 3.0, 0.5 Hz, H-2'), 3.40 (s, 3 H, OCH_3), 1.47 (s, 3 H, isopropylidene CH_3), 1.34 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.16 (Ar), 138.06 (Ar), 128.34 (Ar × 2), 128.32 (Ar × 2), 127.87 (Ar × 2), 127.79 (Ar × 2), 127.70 (Ar), 127.57 (Ar), 109.71 (isopropylidene C), 107.96 (C-1), 101.11 (C-1'), 87.39 (C-2), 83.99 (C-3), 80.43 (C-4), 77.42 (C-4'), 75.10 (C-5'), 73.41 ($PhCH_2$), 72.37 ($PhCH_2$), 69.74 (C-5), 65.41 (C-6'), 55.16 (OCH_3), 54.92 (C-2'), 54.16 (C-3'), 26.64 (isopropylidene CH_3), 25.15 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{29}H_{36}O_9Na$ 551.2252, found 551.2254.

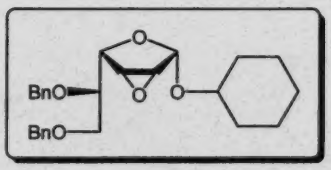
_n_-Octyl 2,3-anhydro-5,6-di-_O_-benzyl-α-D-gulofuranoside (39).



The glycosylation was carried out following the general protocol, and **39** was isolated by chromatography (4:1, hexanes:EtOAc) as a colorless oil. R_f 0.42 (4:1, hexanes: EtOAc); $[\alpha]_D$ +28.9 (c 0.4, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.27 (m, 10 H, Ar), 5.08 (d, 1 H, J = 0.5 Hz, H-1), 4.79 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.74 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.60 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.55 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.10 (dd, 1 H, J = 7.1, 0.8 Hz, H-4), 3.91 (ddd, 1 H, J = 7.1, 4.9, 3.6 Hz, H-5), 3.82-3.74 (m, 3 H, H-6 × 2, octyl OCH_2), 3.67 (dd, 1 H, J = 3.0, 0.8 Hz, H-3), 3.65 (dd, 1 H, J = 3.0, 0.5 Hz, H-2), 3.58 (ddd, 1 H, J = 9.6, 7.0, 7.0 Hz, octyl OCH_2), 1.68-1.60 (m, 2 H, octyl

CH_2), 1.40-1.24 (m, 10 H, octyl CH_2), 0.90-0.87 (dd, 3 H, J = 7.0, 7.0 Hz, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.72 (Ar), 138.22 (Ar), 128.36 (Ar × 2), 128.26 (Ar × 2), 127.85 (Ar × 2), 127.68 (Ar × 2), 127.61 (Ar), 127.50 (Ar), 101.48 (C-1), 78.50 (C-5), 78.01 (C-4), 73.46 ($PhCH_2$), 73.16 ($PhCH_2$), 70.54 (C-6), 69.47 (octyl OCH_2), 55.50 (C-2), 54.77 (C-3), 31.83 (octyl CH_2), 29.79 (octyl CH_2), 29.41 (octyl CH_2), 29.27 (octyl CH_2), 26.04 (octyl CH_2), 22.66 (octyl CH_2), 14.09 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{28}H_{38}O_5Na$ 477.2612, found 477.26.13

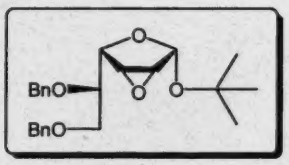
Cyclohexyl 2,3-anhydro-5,6-di-*O*-benzyl-α-D-gulofuranoside (40).



The glycosylation was carried out following the general protocol, and **40** was purified by chromatography (4:1, hexanes:EtOAc) as a colorless oil. R_f 0.34 (4:1, hexanes: EtOAc); $[\alpha]_D$ -24.8 (*c* 0.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.26 (m, 10 H, Ar), 5.19 (s, 1 H, H-1), 4.78 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.74 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.60 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.55 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.08 (dd, 1 H, J = 7.1, 0.8 Hz, H-4), 3.91 (ddd, 1 H, J = 7.1, 4.9, 3.4 Hz, H-5), 3.80 (dd, 1 H, J = 10.8, 3.4 Hz, H-6), 3.77 (dd, 1 H, J = 10.8, 4.9 Hz, H-6), 3.65 (dd, 1 H, J = 2.9, 0.8 Hz, H-3), 3.64-3.60 (m, 1 H, cyclohexyl OCH), 3.63 (d, 1 H, J = 2.9 Hz, H-2), 2.02-1.92 (m, 2 H, cyclohexyl CH_2), 1.80-1.74 (m, 2 H, cyclohexyl CH_2), 1.60-1.54 (m, 1 H, cyclohexyl CH_2), 1.48-1.32 (m, 2 H, cyclohexyl CH_2), 1.30-1.15 (m, 3 H, cyclohexyl CH_2); ^{13}C NMR (125 MHz, CD_3Cl, δ_C) 138.76 (Ar), 138.25 (Ar), 128.35 (Ar × 2), 128.26

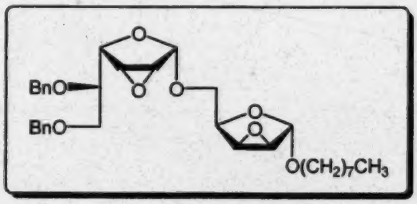
(Ar × 2), 127.85 (Ar × 2), 127.67 (Ar × 2), 127.59 (Ar), 127.48 (Ar), 100.37 (C-1), 78.58 (C-5), 78.06 (C-4), 77.97 (cyclohexyl OCH), 73.44 ($PhCH_2$), 73.17 ($PhCH_2$), 70.61 (C-6), 56.04 (C-2), 54.63 (C-3), 33.60 (cyclohexyl CH_2), 32.52 (cyclohexyl CH_2), 25.56 (cyclohexyl CH_2), 24.32 (cyclohexyl CH_2 × 2). HRMS (ESI) calcd. for (M+Na) $C_{26}H_{32}O_5Na$ 447.2141, found 447.2142.

***tert*-Butyl 2,3-anhydro-5,6-di-*O*-benzyl-α-D-gulofuranoside (41).**



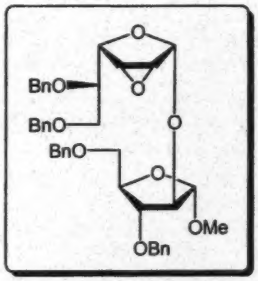
The glycosylation was carried out following the general protocol, and **41** was isolated by chromatography (4:1, hexanes:EtOAc) as a colorless oil. R_f 0.22 (4:1, hexanes: EtOAc); $[\alpha]_D$ -21.0 (*c* 0.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.25 (m, 10 H, Ar), 5.25 (s, 1 H, H-1), 4.79 (d, 1 H, J = 11.9 Hz, $PhCH_2$), 4.73 (d, 1 H, J = 11.9 Hz, $PhCH_2$), 4.60 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.56 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.06 (dd, 1 H, J = 7.2, 0.8 Hz, H-4), 3.92 (ddd, 1 H, J = 7.2, 5.0, 3.5 Hz, H-5), 3.81 (dd, 1 H, J = 10.9, 3.5 Hz, H-6), 3.77 (dd, 1 H, J = 10.9, 5.0 Hz, H-6), 3.63 (dd, 1 H, J = 3.0, 0.8 Hz, H-3), 3.57 (d, 1 H, J = 3.0 Hz, H-2), 1.32 (s, 9 H, *t*-butyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.87 (Ar), 138.30 (Ar), 128.34 (Ar × 2), 128.23 (Ar × 2), 127.81 (Ar × 2), 127.64 (Ar × 2), 127.56 (Ar), 127.43 (Ar), 96.30 (C-1), 78.77 (C-5), 78.15 (C-4), 75.55 (*t*-butyl $\underline{C}(CH_3)$), 73.40 ($PhCH_2$), 73.23 ($PhCH_2$), 70.76 (C-6), 56.69 (C-2), 54.18 (C-3), 28.65 (*t*-butyl CH_3 × 3). HRMS (ESI) calcd. for (M+Na) $C_{24}H_{30}O_5Na$ 421.1986, found 421.1989.

***n*-Octyl 2,3-anhydro-5-*O*-(2,3-anhydro-5,6-di-*O*-benzyl-α-D-gulofuranosyl)-α-D-lyxofuranoside (42).**



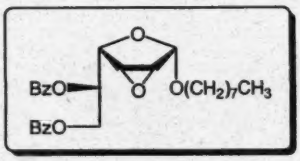
The glycosylation was carried out following the general protocol, and **42** was isolated by chromatography (3:1, hexanes:EtOAc) as a colorless oil. R_f 0.27 (3:1, hexanes:EtOAc); $[\alpha]_D$ +27.6 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.25 (m, 10 H, Ar), 5.17 (s, 1 H, H-1'), 5.04 (s, 1 H, H-1), 4.77 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.73 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.60 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.55 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.23 (dd, 1 H, J = 7.8, 5.4 Hz, H-4), 4.12 (d, 1 H, J = 7.0 Hz, H-4'), 3.94 (dd, 1 H, J = 9.9, 5.4 Hz, H-5), 3.89 (ddd, 1 H, J = 7.0, 4.8, 3.7 Hz, H-5'), 3.82-3.72 (m, 5 H, H-5, H-3', H-6'×2, octyl OCH_2), 3.68 (s, 2 H, H-2, H-3), 3.66 (d, 1 H, J = 2.8 Hz, H-2'), 3.45 (ddd, 1 H, J = 9.5, 6.6, 6.6 Hz, octyl OCH_2), 1.62-1.54 (m, 2 H, octyl CH_2), 1.35-1.24 (m, 10 H, octyl CH_2), 0.90-0.86 (dd, 3 H, J = 6.9, 6.9 Hz, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.58 (Ar), 138.14 (Ar), 128.38 (Ar×2), 128.30 (Ar×2), 127.87 (Ar×2), 127.69 (Ar×2), 127.64 (Ar), 127.54 (Ar), 101.50 (C-1'), 101.17 (C-1), 78.33 (C-5'), 78.13 (C-4), 74.63 (C-4'), 73.49 (Bn CH_2), 73.07 (Bn CH_2), 70.35 (C-6'), 68.57 (octyl OCH_2), 66.84 (C-5'), 56.55 (C-2'), 55.28 (C-2), 54.75 (C-3), 54.44 (C-3'), 31.80 (octyl CH_2), 29.63 (octyl CH_2), 29.35 (octyl CH_2), 29.23 (octyl CH_2), 26.04 (octyl CH_2), 22.64 (octyl CH_2), 14.08 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{33}H_{44}O_8Na$ 591.2928, found 591.2926.

Methyl 3,5-di-*O*-benzyl-2-*O*-(2,3-anhydro-5,6-*O*-benzyl-1-α-D-gulofuranosyl)-α-D-arabinofuranoside (43).



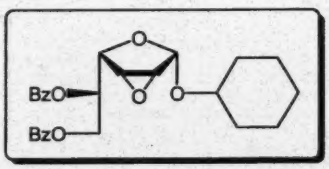
The glycosylation was carried out following the general protocol, and **43** was purified by chromatography (3:1, hexanes:EtOAc) as a colorless oil. R_f 0.21 (3:1, hexanes:EtOAc); $[\alpha]_D$ +53.7 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.36-7.25 (m, 20 H, Ar), 5.06 (s, 1 H, H-1), 4.98 (s, 1 H, H-1'), 4.75 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.69 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.64-4.53 (m, 6 H, $PhCH_2$), 4.24 (d, 1 H, J = 2.8 Hz, H-2), 4.20 (ddd, 1 H, J = 6.8, 5.4, 4.0 Hz, H-4), 4.01 (dd, 1 H, J = 7.0, 0.6 Hz, H-4'), 3.94 (dd, 1 H, J = 6.8, 2.8 Hz, H-3), 3.89 (ddd, 1 H, J = 7.0, 4.7, 3.7 Hz, H-5'), 3.80-3.74 (m, 2 H, H-6'×2), 3.68-3.61 (m, 3 H, H-5×2, H-3'), 3.52 (d, 1 H, J = 3.0 Hz, H-2'), 3.36 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.56 (Ar), 138.17 (Ar), 138.14 (Ar), 137.99 (Ar), 128.46 (Ar × 2), 128.38 (Ar × 2), 128.33 (Ar × 2), 128.30 (Ar × 2), 127.85 (Ar × 2), 127.80 (Ar × 2), 127.73 (Ar × 3), 127.69 (Ar × 2), 127.65 (Ar), 127.59 (Ar), 127.55 (Ar), 107.80 (C-1), 101.37 (C-1'), 88.14 (C-2), 83.93 (C-3), 80.41 (C-4), 78.66 (C-5'), 78.34 (C-4'), 73.52 ($PhCH_2$), 73.42 ($PhCH_2$), 73.27 ($PhCH_2$), 72.39 ($PhCH_2$), 70.51 (C-6'), 69.79 (C-5), 55.33 (C-2'), 55.06 (OCH_3), 54.72 (C-3'). HRMS (ESI) calcd. for (M+Na) $C_{40}H_{44}O_9Na$ 691.2878, found 691.2878.

_n_-Octyl 2,3-anhydro-5,6-di-_O_-benzoyl-α-D-gulofuranoside (44).



The glycosylation was carried out following the general protocol, and **44** was isolated by chromatography (4:1, hexanes:EtOAc) as a white foam. R_f 0.26 (4:1, hexanes: EtOAc); $[\alpha]_D$ +44.1 (*c* 0.3, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.10-8.07 (m, 2 H, Ar), 8.03 (m, 2 H, Ar), 7.59-7.50 (m, 2 H, Ar), 7.46-7.39 (m, 4 H, Ar), 5.77 (dd, 1 H, J = 10.1, 5.5 Hz, H-5), 5.13 (d, 1 H, J = 0.5 Hz, H-1), 4.82-4.78 (m, 2 H, H-6 × 2), 4.24 (dd, 1 H, J = 5.5, 0.8 Hz, H-4), 3.82 (dd, 1 H, J = 3.0, 0.8 Hz, H-3), 3.77 (ddd, 1H, J = 9.6, 6.6, 6.6 Hz, octyl OCH_2), 3.71 (dd, 1 H, J = 3.0, 0.5 Hz, H-2), 3.62 (ddd, 1 H, J = 9.6, 6.9, 6.9 Hz, octyl OCH_2), 1.65-1.59 (m, 2 H, octyl CH_2), 1.38-1.22 (m, 10 H, octyl CH_2), 0.87 (dd, 3 H, J = 7.0, 7.0 Hz, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.10 (C=O), 165.80 (C=O), 133.17 (Ar), 133.08 (Ar), 129.86 (Ar × 2), 129.84 (Ar), 129.79 (Ar), 129.69 (Ar × 2), 128.38 (Ar × 4), 101.23 (C-1), 74.79 (C-4), 71.63 (C-5), 69.30 (octyl OCH_2), 63.39 (C-6), 55.38 (C-2), 54.13 (C-3), 31.82 (octyl CH_2), 29.79 (octyl CH_2), 29.36 (octyl CH_2), 29.24 (octyl CH_2), 29.75 (octyl CH_2), 22.64 (octyl CH_2), 14.08 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{28}H_{34}O_7Na$ 505.2197, found 505.2197.

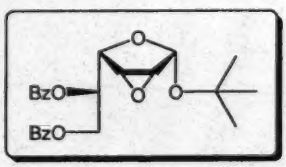
Cyclohexyl 2,3-anhydro-5,6-di-_O_-benzoyl-α-D-gulofuranoside (45).



The glycosylation was carried out following the general protocol, and **45** was isolated by chromatography (4:1,

hexanes:EtOAc) as a white foam. R_f 0.19 (4:1, hexanes: EtOAc); $[\alpha]_D$ +67.9 (*c* 0.7, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.10-8.07 (m, 2 H, Ar), 8.03-8.00 (m, 2 H, Ar), 7.58-7.51 (m, 2 H, Ar), 7.46-7.39 (m, 4 H, Ar), 5.78 (ddd, 1 H, J = 5.4, 5.0, 5.0 Hz, H-5), 5.22 (d, 1 H, J = 0.5 Hz, H-1), 4.80 (d, 2 H, J = 5.0 Hz, H-6 × 2), 4.22 (dd, 1 H, J = 5.4, 0.9 Hz, H-4), 3.80 (dd, 1 H, J = 2.9, 0.9 Hz, H-3), 3.70 (dd, 1 H, J = 2.9, 0.5 Hz, H-2), 3.69-3.60 (m, 1 H, cyclohexyl OCH), 1.99-1.87 (m, 2 H, cyclohexyl CH_2), 1.78-1.70 (m, 2 H, cyclohexyl CH_2), 1.57-1.48 (m, 1 H, cyclohexyl CH_2), 1.45-1.15 (m, 5 H, cyclohexyl CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.13 (C=O), 165.83 (C=O), 133.15 (Ar), 133.05 (Ar), 129.86 (Ar × 2), 129.82 (Ar × 2), 129.69 (Ar × 2), 129.38 (Ar × 2), 128.37 (Ar × 2), 100.15 (C-1), 77.64 (cyclohexyl OCH), 74.81 (C-4), 71.66 (C-5), 63.46 (C-6), 55.97 (C-2), 54.15 (C-3), 33.45 (cyclohexyl CH_2), 32.57 (cyclohexyl CH_2), 25.53 (cyclohexyl CH_2), 24.20 (cyclohexyl CH_2), 24.16 (cyclohexyl CH_2). HRMS (ESI) calcd. for (M+Na) $C_{26}H_{28}O_7Na$ 475.1727, found 475.1730.

***tert*-Butyl 2,3-anhydro-5,6-di-*O*-benzoyl-α-D-gulofuranoside (46).**



The glycosylation was carried out following the general protocol, and **46** was isolated by chromatography (4:1, hexanes:EtOAc) as a white foam. R_f 0.17 (4:1, hexanes: EtOAc); $[\alpha]_D$ +82.53 (*c* 0.4, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.10-8.07 (m, 2 H, Ar), 8.03-8.00 (m, 2 H, Ar), 7.58-7.51 (m, 2 H, Ar), 7.46-7.38 (m, 4 H, Ar), 5.77 (ddd, 1 H, J = 5.9, 5.6, 4.5 Hz, H-5), 5.29 (d, 1 H, J = 0.6 Hz, H-1), 4.84-4.80 (m, 2 H, H-6 × 2),

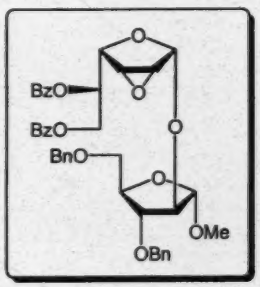
4.21 (dd, 1 H, J = 5.6, 0.9 Hz, H-4), 3.79 (dd, 1 H, J = 2.9, 0.9 Hz, H-3), 3.65 (dd, 1 H, J = 2.9, 0.6 Hz, H-2), 1.27 (s, 9 H, t-butyl CH_3 × 3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.13 (C=O), 165.83 (C=O), 133.12 (Ar), 133.01 (Ar), 129.93 (Ar), 129.91 (Ar), 129.85 (Ar × 2), 129.69 (Ar × 2), 128.37 (Ar × 2), 128.35 (Ar × 2), 96.37 (C-1), 75.76 (t-butyl $\underline{C}(CH_3)$), 74.99 (C-4), 71.88 (C-5), 63.50 (C-6), 56.85 (C-2), 53.72 (C-3), 28.61 (t-butyl CH_3 × 3). HRMS (ESI) calcd. for (M+Na) $C_{24}H_{26}O_7Na$ 449.1571, found 449.1573.

n-Octyl 2,3-anhydro-5-*O*-(2,3-anhydro-5,6-di-*O*-benzoyl-α-D-gulofuranosyl)-α-D-lyxofuranoside (47).

The glycosylation was carried out following the general protocol, and **47** was isolated by chromatography (2:1, hexanes:EtOAc) as a white foam. R_f 0.18 (2:1, hexanes:EtOAc); $[\alpha]_D$ +42.6 (c 0.6, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.10-8.07 (m, 2 H, Ar), 8.03-8.00 (m, 2 H, Ar), 7.58-7.52 (m, 2 H, Ar), 7.46-7.39 (m, 4 H, Ar), 5.78 (ddd, 1 H, J = 5.5, 5.1, 5.1 Hz, H-5'), 5.23 (d, 1 H, J = 0.5 Hz, H-1'), 5.03 (s, 1 H, H-1), 4.78 (d, 2 H, J = 5.1 Hz, H-6' × 2), 4.27 (dd, 1 H, J = 5.5, 0.9 Hz, H-4'), 4.22 (dd, 1 H, J = 6.9, 6.0 Hz, H-4), 3.94-3.87 (m, 2 H, H-5 × 2), 3.84 (dd, 1 H, J = 2.9, 0.9 Hz, H-3'), 3.82 (dd, 1 H, J = 2.9, 0.5 Hz, H-2'), 3.75 (d, 1 H, J = 2.8 Hz, H-3), 3.72 (ddd, 1 H, J = 9.5, 6.7, 6.7 Hz, octyl OCH_2), 3.64 (d, 1 H, J = 2.8 Hz, H-2), 3.43 (ddd, 1 H, J = 9.5, 6.8, 6.8, octyl OCH_2), 1.58-1.52 (m, 2 H, octyl CH_2), 1.35-1.23 (m, 10 H, octyl CH_2), 0.88-0.86 (m, 3 H, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C)

166.08 (C=O), 165.78 (C=O), 133.20 (Ar), 133.14 (Ar), 129.836 (Ar × 2), 129.76 (Ar × 2), 129.69 (Ar × 2), 128.41 (Ar × 4), 101.27 (C-1'), 101.18 (C-1), 75.02 (C-4'), 74.76 (C-4), 71.46 (C-5'), 68.50 (octyl OCH_2), 66.69 (C-5), 63.30 (C-6'), 56.45 (C-2), 55.28 (C-3), 54.41 (C-2'), 54.19 (C-3'), 31.80 (octyl CH_2), 29.61 (octyl CH_2), 29.34 (octyl CH_2), 29.22 (octyl CH_2), 26.02 (octyl CH_2), 22.63 (octyl CH_2), 14.08 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{33}H_{40}O_{10}Na$ 619.2514, found 619.2518.

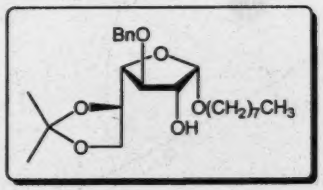
Methyl 3,5-di-*O*-benzyl-2-*O*-(2,3-anhydro-5,6-*O*-benzoyl-α-D-gulofuranosyl)-α-D-arabinofuranoside (48).



The glycosylation was carried out following the general protocol, and **48** was isolated by chromatography (2:1, hexanes:EtOAc) as a colorless syrup. R_f 0.26 (2:1, hexanes:EtOAc); $[\alpha]_D$ +59.3 (*c* 0.6, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.09-8.06 (m, 2 H, Ar), 8.04-8.00 (m, 2 H, Ar), 7.58-7.53 (m, 2 h, Ar), 7.45-7.40 (m, 4 H, Ar), 7.35-7.24 (m, 10 H, Ar), 5.78 (ddd, 1 H, J = 5.7, 5.0, 5.0 Hz, H-5'), 5.03 (s, 1 H, H-1), 5.00 (s, 1 H, H-1'), 4.76 (d, 2 H, J = 5.0 Hz, H-6' × 2), 4.64-4.56 (m, 4 H, $PhCH_2$ × 2), 4.27 (d, 1 H, J = 5.7 Hz, H-4'), 4.22 (d, 1 H, J = 3.0 Hz, H-2), 4.20-4.16 (m, 1 H, H-4), 3.93 (dd, 1 H, J = 6.9, 3.0 Hz, H-3), 3.82 (d, 1 H, J = 2.9 Hz, H-3'), 3.67 (dd, 1 H, J = 10.8, 3.7 Hz, H-5), 3.64 (dd, 1 H, J = 10.8, 5.4 Hz, H-5), 3.61 (d, 1 H, J = 2.9 Hz, H-2'), 3.28 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.04 (C=O), 165.73 (C=O), 138.20 (Ar), 138.06 (Ar), 133.22 (Ar), 133.18 (Ar), 129.90 (Ar×2), 129.71 (Ar×2),

129.76 (Ar), 129.66 (Ar), 128.44 (Ar × 2), 128.42 (Ar × 2), 128.34 (Ar × 2), 128.33 (Ar × 2), 127.86 (Ar × 2), 127.81 (Ar × 2), 127.69 (Ar), 127.57 (Ar), 107.80 (C-1), 101.40 (C-1'), 88.24 (C-2), 84.13 (C-3), 80.13 (C-4), 75.38 (C-4'), 73.42 ($PhCH_2$), 72.49 ($PhCH_2$), 71.50 (C-5'), 69.76 (C-5), 63.30 (C-6'), 55.47 (C-2'), 55.03 (OCH_3), 54.33 (C-3'). HRMS (ESI) calcd. for (M+Na) $C_{40}H_{40}O_{11}Na$ 719.2463, found 719.2461.

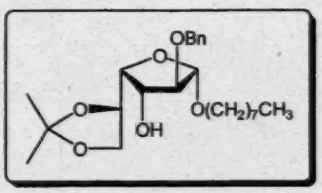
_n_-Octyl 3-_O_-benzyl-5,6-_O_-isopropylidene-α-D-gulofuranoside (52a).



Compound **26** was subjected to the general procedure to open the epoxide, yielding seperable **52a** and **52b** as colorless oils. **52a**: R_f 0.46 (4:1, hexanes:EtOAc); $[\alpha]_D$ +36.5 (*c* 0.2, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.27 (m, 5 H, Ar), 4.98 (d, 1 H, J = 4.8 Hz, H-1), 4.87 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.62 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.27 (ddd, 1 H, J = 9.8, 6.2, 4.8 Hz, H-2), 4.11 (dd, 1 H, J = 7.3, 7.3 Hz, H-4), 3.91-3.84 (m, 3 H, H-5, H-6, octyl OCH_2), 3.80-3.74 (m, 2 H, H-3, H-6), 3.48 (ddd, 1 H, J = 9.6, 6.7, 6.7 Hz, octyl OCH_2), 2.67 (d, 1 H, J = 9.8 Hz, OH), 1.64-1.54 (m, 2 H, octyl CH_2), 1.43 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3), 1.38-1.24 (m, 10 H, octyl CH_2), 0.92-0.87 (m, 3 H, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.63 (Ar), 128.43 (Ar × 2), 128.02 (Ar), 127.86 (Ar × 2), 109.71 (isopropylidene C), 101.64 (C-1), 83.75 (C-3), 81.88 (C-5), 78.23 (C-4), 78.00 (C-2), 71.69 ($PhCH_2$), 68.75 (octyl OCH_2), 65.21 (C-6), 31.79 (octyl CH_2), 29.52 (octyl CH_2), 29.34 (octyl CH_2), 29.20 (octyl CH_2), 26.60 (isopropylidene CH_3), 26.06 (octyl CH_2), 25.51 (isopropylidene CH_3), 22.63 (octyl

CH_2), 14.07 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{24}H_{38}O_6Na$ 445.2561, found 445.2559.

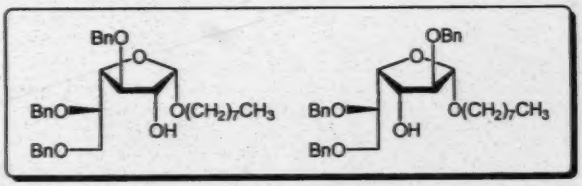
***n*-Octyl 2-*O*-benzyl-5,6-*O*-isopropylidene-α-D-idofuranoside (52b).**



52b: R_f 0.38 (4:1, hexanes:EtOAc); $[\alpha]_D$ +35.6 (*c* 0.26, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.29 (m, 5 H, Ar), 5.09 (s, 1 H, H-1), 4.61 (s, 2 H, $PhCH_2$), 4.32 (ddd, 1 H, J = 7.3, 7.2, 7.2 Hz, H-5), 4.24-4.19 (m, 2 H, H-4, H-6), 4.08 (br, 1 H, H-3), 3.94 (s, 1 H, H-2), 3.85 (ddd, 1 H, J = 9.6, 6.8, 6.8 Hz, octyl OCH_2), 3.73 (dd ,1 H, J = 8.3, 7.2 Hz, H-6), 3.42 (ddd, 1 H, J = 9.6, 6.6, 6.6 Hz, octyl OCH_2), 2.99 (d, 1 H, J = 11.3 Hz, OH), 1.60-1.52 (m, 2 H, octyl CH_2), 1.52 (s, 3 H, isopropylidene CH_3), 1.45 (s, 3 H, isopropylidene CH_3), 1.35-1.24 (m, 10 H, octyl CH_2), 0.92-0.85 (m, 3 H, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.32 (Ar), 128.53 (Ar × 2), 128.01 (Ar), 127.68 (Ar × 2), 109.69 (isopropylidene C), 105.56 (C-1), 86.20 (C-2), 84.86 (C-4), 76.98 (C-5), 74.42 (C-3), 71.99 ($PhCH_2$), 68.17 (octyl OCH_2), 66.12 (C-6), 31.79 (octyl CH_2), 29.45 (octyl CH_2), 29.30 (octyl CH_2), 29.19 (octyl CH_2), 26.66 (isopropylidene CH_3), 26.07 (octyl CH_2), 25.52 (isopropylidene CH_3), 22.63 (octyl CH_2), 14.07 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{24}H_{38}O_6Na$ 445.2561, found 445.2562.

***n*-Octyl 3,5,6-tri-*O*-benzyl-α-D-galactofuranoside (53a/53b).**

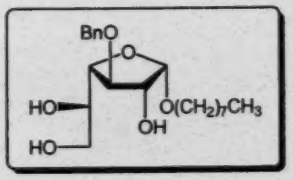
Compound **39** was subjected to the general procedure to open the epoxide, yielding a mixture of **53a** and **53b** as



colorless oils. R_f 0.41 (4:1, hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.43-7.25 (m, 15 H, Ar), 5.08 (s, 0.74 H, ido H-1), 4.96 (d, 0.26 H, J = 4.7 Hz, gal H-1), 4.82-4.74 (m, 2 H, $PhCH_2$), 4.63-4.52 (m, 4 H, $PhCH_2$), 4.40 (dd, 0.74 H, J = 7.4, 3.8 Hz, ido H-4), 4.24 (br, 0.26 H, gal H-2), 4.12 (br, 0.74 H, ido H-3), 4.05-3.99 (m, 0.52 H, gal H-3, gal H-4), 3.74 (s, 0.74 H, ido H-2), 3.71 (ddd, 0.74 H, J = 7.4, 4.6, 4.6 Hz, ido H-5), 3.80-3.64 (m, 3.26 H, gal H-5, gal H-6 × 2, ido H-6 × 2, octyl OCH_2), 3.45-3.40 (m, 0.26 H, gal octyl OCH_2), 3.39 (ddd, 0.74 H, J = 9.5, 6.6, 6.6 Hz, ido octyl OCH_2), 3.27 (d, 0.74 H, J = 9.2 Hz, ido OH), 2.71 (d, 0.26 H, J = 7.0 Hz, gal OH), 1.58-1.47 (m, 2 H, octyl CH_2), 1.34-1.25 (m, 10 H, octyl CH_2), 0.92-0.89 (m, 3 H, octyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.72 (Ar), 138.27 (Ar), 138.07 (Ar), 138.04 (Ar), 137.51 (Ar), 128.47 (Ar), 128.40 (Ar), 128.35 (Ar), 128.26 (Ar), 128.21 (Ar), 127.96 (Ar), 127.91 (Ar), 127.86 (Ar), 127.82 (Ar), 127.73 (Ar), 127.68 (Ar), 127.61 (Ar), 127.57 (Ar), 127.49 (Ar), 127.46 (Ar), 105.57 (ido C-1), 101.21 (gal C-1), 86.70 (ido C-2), 83.91 (ido C-4), 83.34 (gal C-3), 81.30 (gal C-4), 79.03 (gal C-5), 78.49 (ido C-5), 77.76 (gal C-2), 74.06 (ido C-3), 73.60 (ido $PhCH_2$), 73.44 (gal $PhCH_2$), 73.14 (gal $PhCH_2$), 72.88 (ido $PhCH_2$), 71.84 (ido $PhCH_2$), 71.75 (gal $PhCH_2$), 70.58 (gal C-6), 70.26 (ido C-6), 68.50 (gal octyl OCH_2), 68.14 (ido octyl OCH_2), 31.82 (octyl CH_2), 29.51 (gal octyl CH_2),

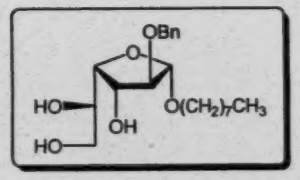
29.46 (ido octyl CH_2), 29.44 (gal octyl CH_2), 29.38 (ido octyl CH_2), 29.24 (octyl CH_2), 26.14 (octyl CH_2), 22.66 (octyl CH_2), 14.11 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{35}H_{46}O_6Na$ 585.3187, found 535.3184.

_n_-Octyl 3-_O_-benzyl-α-D-galactofuranoside (54a).



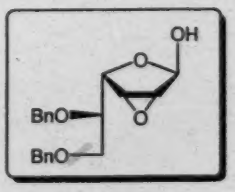
Compound **44** was subjected to the general procedure to open the epoxide, yielding **54a** and **54b** as colorless oils. **54a**: R_f 0.30 (1:1, hexanes:EtOAc); $[\alpha]_D$ +30.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.38-7.25 (m, 5 H, Ar), 4.87 (d, 1 H, J = 4.6 Hz, H-1), 4.82 (d, 1 H, J = 12.7 Hz, $PhCH_2$), 4.62 (d, 1 H, J = 11.6 Hz, $PhCH_2$), 4.17 (dd, 1 H, J = 6.8, 4.6 Hz, H-2), 4.09 (dd, 1 H, J = 6.8, 6.2 Hz, H-3), 3.89 (dd, 1 H, J = 6.2, 5.0 Hz, H-4), 3.80 (ddd, 1 H, J = 9.6, 6.9, 6.9 Hz, octyl OCH_2), 3.62-3.54 (m, 2 H, H-5, H-6), 3.51-3.45 (m, 2 H, H-6, octyl OCH_2), 1.65-1.58 (m, 2 H, octyl CH_2), 1.40-1.25 (m, 10 H, octyl CH_2), 0.95-0.85 (m, 3 H, octyl CH_3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 139.62 (Ar), 129.34 (Ar × 2), 128.98 (Ar × 2), 128.71 (Ar), 103.47 (C-1), 84.09 (C-3), 82.62 (C-4), 79.01 (C-2), 74.52 (C-5), 73.14 ($PhCH_2$), 69.99 (octyl OCH_2), 64.13 (C-6), 33.02 (octyl CH_2), 30.72 (octyl CH_2), 30.60 (octyl CH_2), 30.41 (octyl CH_2), 27.19 (octyl CH_2), 23.72 (octyl CH_2), 14.43 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{21}H_{34}O_6Na$ 405.2248, found 405.2246.

***n*-Octyl 2-*O*-benzyl-α-D-idofuranoside (54b).**



54b: R_f 0.13 (1:1, hexanes:EtOAc); $[\alpha]_D$ +19.6 (*c* 1.4, CH_2Cl_2); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.35-7.27 (m, 5 H, Ar), 4.97 (d, 1 H, J = 1.5 Hz, H-1), 4.64 (d, 1 H, J = 11.9 Hz, $PhCH_2$), 4.60 (d, 1 H, J = 11.9 Hz, $PhCH_2$), 4.24 (dd, 1 H, J = 5.3, 2.4 Hz, H-3), 4.15 (dd, 1 H, J = 5.3, 5.2 Hz, H-4), 3.92-3.90 (m, 1 H, H-2), 3.88 (ddd, 1 H, J = 5.9, 5.4, 5.2 Hz, H-5), 3.77 (ddd, 1 H, J = 9.6, 6.7, 6.7 Hz, octyl OCH_2), 3.65 (dd, 1 H, J = 11.2, 5.4 Hz, H-6), 3.60 (dd, 1 H, J = 11.2, 5.9 Hz, H-6), 3.42 (ddd, 1 H, J = 9.6, 6.6, 6.6 Hz, octyl OCH_2), 1.60-1.52 (m, 2 H, octyl CH_2), 1.38-1.27 (m, 10 H, octyl CH_2), 0.91-0.87 (m, 3 H, octyl CH_3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 139.27 (Ar), 129.41 (Ar × 2), 128.96 (Ar × 2), 128.83 (Ar), 107.95 (C-1), 89.83 (C-2), 83.09 (C-4), 75.82 (C-3), 72.98 ($PhCH_2$), 72.34 (C-5), 69.63 (octyl OCH_2), 64.37 (C-6), 33.00 (octyl CH_2), 30.63 (octyl CH_2), 30.50 (octyl CH_2), 30.42 (octyl CH_2), 27.27 (octyl CH_2), 23.72 (octyl CH_2), 14.43 (octyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{21}H_{34}O_6Na$ 405.2248, found 405.2248.

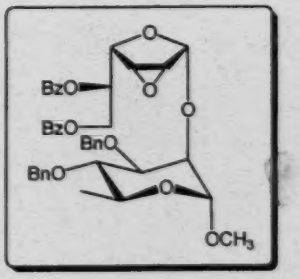
2,3-anhydro-5,6-di-*O*-benzyl-β-D-galactofuranoside (63).



To a solution of donor **4** (110 mg, 0.25 mmol) in CH_3CN (5 mL) and H_2O (1 mL) was added *N*-iodosuccinimide (70 mg, 0.3 mmol) and silver triflate (19 mg, 0.07 mmol) at 0 °C. After stirring for 15 min at 0 °C, the reaction mixture was neutralized by addition of triethylamine, and diluted with CH_2Cl_2 (20 mL)and filtered through Celite. The filtrate was concentrated to

give a crude residue that was purified by chromatography (2:1, hexanes:EtOAc) to provide **63** (65 mg, 77%) as a colorless semi-solid. R_f 0.48 (1:1, hexanes:EtOAc); $[\alpha]_D$ +16.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.43-7.28 (m, 10 H, Ar), 5.39 (s, 1 H, H-1), 4.78 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.71 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.60 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.54 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.34 (d, 1 H, J = 7.0 Hz, H-4), 3.86 (br, 1 H, OH), 3.81 (ddd, 1 H, J = 7.0, 5.0, 3.8 Hz, H-5), 3.78-3.66 (m, 3 H, H-3, H-6 × 2), 3.60 (d, 1 H, J = 2.8 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 138.40 (Ar), 138.03 (Ar), 128.42 (Ar × 2), 128.32 (Ar × 2), 127.98 (Ar), 127.93 (Ar × 2), 127.72 (Ar × 2), 127.64 (Ar), 95.43 (C-1), 78.23 (C-5), 77.37 (C-4), 73.49 ($PhCH_2$), 73.03 ($PhCH_2$), 70.20 (C-6), 56.52 (C-2), 54.07 (C-3). HRMS (ESI) calcd. for (M+Na) $C_{20}H_{22}O_5Na$ 365.1359, found 365.1358.

Methyl 3,4-di-*O*-benzyl-2-*O*-(2,3-anhydro-5,6-di-*O*-benzoyl-α-D-gulofuranosyl)-α-L-rhamnopyranoside (49).

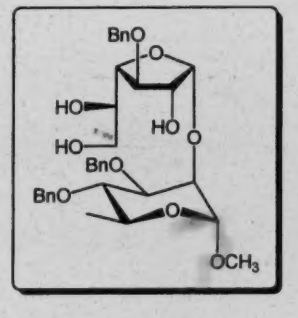


The glycosylation of thioglycoside **5** (472 mg, 0.99 mmol) and sugar acceptor **33**[127] (351 mg, 0.98 mmole) was carried out following the general protocol, and the crude reaction mixture was purified by chromatography (2:1, hexanes:EtOAc) to give disaccharide **49** (217 mg, 69%) as a colorless syrup. R_f 0.26 (2:1, hexanes:EtOAc); $[\alpha]_D$ +14.7 (*c* 2.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.08 (d, 2 H, J = 8.4 Hz, Ar), 8.00 (d, 2 H, J = 8.3 Hz, Ar), 7.60-7.54 (m, 2 H, Ar), 7.48-7.40 (m, 4 H, Ar), 7.36-7.20 (m, 10

H, Ar), 5.88-5.84 (m, 1 H, H-5'), 5.38 (s, 1 H, H-1'), 4.97(d, 1 H, J = 10.9 Hz, $PhCH_2$), 4.81 (br, 1 H, H-2), 4.77 (dd, 1 H, J = 12.1, 6.6 Hz, H-6'), 4.75 (s, 1 H, H-1), 4.72 (dd, 1 H, J = 12.1, 4.0 Hz, H-6'), 4.68 (d, 1 H, J = 11.2 Hz, $PhCH_2$), 4.63 (d, 1 H, J = 10.9 Hz, $PhCH_2$), 4.50 (d, 1 H, J = 11.2 Hz, $PhCH_2$), 4.20 (d, 1 H, J = 5.0 Hz, H-4'), 3.84 (dd, 1 H, J = 9.3, 3.2 Hz, H-3), 3.78 (d, 1 H, J = 2.9 Hz, H-2'), 3.69 (qd, 1 H, J = 9.2, 6.2 Hz, H-5), 3.63 (d, 1 H, J = 2.9 Hz, H-3'), 3.50 (dd, 1 H, J = 9.3, 9.2 Hz, H-4), 3.39 (s, 3 H, OCH_3), 1.31 (d, 3 H, J = 6.2 Hz, H-6 × 3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.04 (C=O), 165.84 (C=O), 138.78 (Ar), 138.50 (Ar), 133.22 (Ar × 2), 129.94 (Ar × 2), 129.75 (Ar), 129.71 (Ar × 2), 129.62 (Ar), 128.44 (Ar × 2), 128.41 (Ar × 2), 128.31(Ar × 2), 128.22 (Ar × 2), 127.90 (Ar × 2), 127.79 (Ar × 2), 127.52 (Ar), 127.41 (Ar), 100.79 (C-1), 99.94 (C-1'), 80.50 (C-4), 78.78 (C-3), 75.29 ($PhCH_2$), 74.03 (C-4'), 72.09 ($PhCH_2$), 70.94 (C-5'), 70.73 (C-2), 67.49 (C-5), 63.37 (C-6'), 55.41 (C-3'), 54.77 (OCH_3), 53.49 (C-2'), 18.04 (C-6). HRMS (ESI) calcd. for (M+Na) $C_{41}H_{42}O_{11}Na$ 733.2619, found 733.2621.

Methyl 3,4-di-*O*-benzyl-2-*O*-(3-*O*-benzyl-α-D-galactofuranosyl)-α-L-rhamnopyranoside (71).

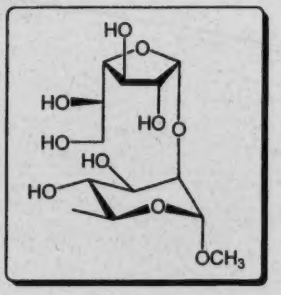
Compound **49** (160 mg, 0.225 mmol) was subjected to the general protocol to open the epoxide, and the resulting residue was purified by chromatography (2:1, hexanes:EtOAc) to give **71** (80 mg, 64%) as colorless oil. R_f 0.29 (1:1, hexanes:EtOAc);



$[\alpha]_D$ +22.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.25 (m, 15 H, Ar), 4.98 (d, 1 H, *J* = 3.8 Hz, H-1'), 4.95 (d, 1 H, *J* = 10.9 Hz, $PhCH_2$), 4.93 (d, 1 H, *J* = 11.1 Hz, $PhCH_2$), 4.80 (d, 1 H, *J* = 11.8 Hz, $PhCH_2$), 4.74 (d, 1 H, *J* = 11.8 Hz, $PhCH_2$), 4.69 (d, 1 H, *J* = 10.9 Hz, $PhCH_2$), 4.68 (d, 1 H, *J* = 11.1 Hz, $PhCH_2$), 4.55 (d, 1 H, *J* = 1.8 Hz, H-1), 4.28-4.24 (m, 2 H, H-2', H-4'), 4.00-3.96 (m, 1 H, H-3'), 4.96-4.94 (m, 1 H, H-2), 3.89 (dd, 1 H, *J* = 9.4, 3.0 Hz, H-3), 3.78 (br, 1 H, OH), 3.67 (qd, 1 H, *J* = 9.5, 6.3 Hz, H-5), 3.62-3.59 (m, 1 H, H-5'), 3.46 (dd, 1 H, *J* = 9.5, 9.4 Hz, H-4), 3.40 (dd, 1 H, *J* = 12.3, 4.3 Hz, H-6'), 3.55-3.51 (m, 4 H, H-6', OCH_3), 1.60 (br, 2 H, OH × 2), 1.30 (d, 3 H, *J* = 6.3 Hz, H-6 × 3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.22 (Ar), 138.05 (Ar), 137.29 (Ar), 128.54 (Ar × 2), 128.42 (Ar × 2), 128.39 (Ar × 2), 128.14 (Ar), 127.98 (Ar × 2), 127.91 (Ar × 2), 127.77 (Ar), 127.73 (Ar × 3), 103.43 (C-1'), 99.06 (C-1), 82.58 (C-4'), 82.27 (C-3'), 80.55 (C-4), 78.52 (C-3), 77.68 (C-2'), 77.54 (C-2), 75.52 ($PhCH_2$), 72.77 ($PhCH_2$), 72.38 ($PhCH_2$), 71.21 (C-5'), 67.88 (C-5), 64.99 (C-6'), 54.83 (OCH_3), 17.95 (C-6). HRMS (ESI) calcd. for (M+Na) $C_{34}H_{42}O_{10}Na$ 633.2670, found 633.2671.

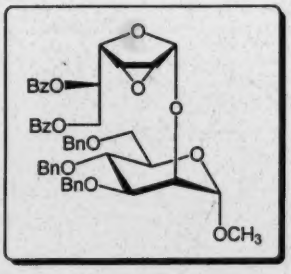
Methyl 2-*O*-(α-D-galactofuranosyl)-α-L-rhamnopyranoside (64).

To a solution of compound **71** (37 mg, 0.06 mmol) in CH_3OH (2 mL) was added 10% Pd/C (5 mg) and the reaction mixture was stirred under hydrogen atmosphere for 5 h. The mixture was filtered through Celite, concentrated and the residue was



purified through Iatrobeads (5:1, CH_2Cl_2:CH_3OH) to yield compound **64** (19 mg, 94%) as a white foam. R_f 0.27 (5:1, CH_2Cl_2:CH_3OH); $[\alpha]_D$ +38.7 (*c* 1.7, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 4.90 (d, 1 H, *J* = 4.8 Hz, H-1'), 4.60 (d, 1 H, *J* = 1.6 Hz, H-1), 4.25 (dd, 1 H, *J* = 8.6, 7.5 Hz, H-3'), 3.92 (dd, 1 H, *J* = 8.6, 4.8 Hz, H-2'), 3.81-3.79 (m, 1 H, H-2), 3.79 (dd, 1 H, *J* = 7.5, 1.8 Hz, H-4'), 3.64-3.57 (m, 4 H, H-3, H-4, H-6' × 2), 3.55 (dq, 1 H, *J* = 9.5, 6.3 Hz, H-5), 3.36-3.32 (m, 4 H, H-5', OCH_3), 1.27 (d, 3 H, *J* = 6.3 Hz, H-6 × 3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 103.69 (C-1'), 101.17 (C-1), 82.57 (C-4'), 80.75 (C-2), 78.65 (C-2'), 74.75 (C-3'), 74.18 (C-5'), 71.55 (C-3, C-4), 69.83 (C-5), 64.41 (C-6'), 55.25 (OCH_3), 17.89 (C-6). HRMS (ESI) calcd. for (M+Na) $C_{13}H_{24}O_{10}Na$ 363.1262, found 363.1263.

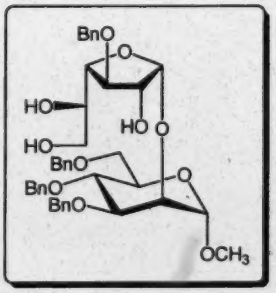
Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3-anhydro-5,6-di-*O*-benzoyl-α-D-gulofuranosyl)-α-D-mannopyranoside (50).



The glycosylation of sulfoxide **6** (140 mg, 0.28 mmol) and acceptor **34**[128] (110 mg, 0.24 mmol) was carried out following the general protocol, and after work-up, the reaction mixture was purified by chromatography (2:1, hexanes:EtOAc) to give **50** (163 mg, 70%) as a white foam. R_f 0.23 (2:1, hexanes:EtOAc); $[\alpha]_D$ +36.9 (*c* 1.4, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.06-8.00 (m, 4 H, Ar), 7.58-7.52 (m, 2 H, Ar), 7.45-7.14 (m, 19 H, Ar), 5.81 (ddd, 1 H, *J* = 5.2, 5.2, 5.2 Hz, H-5'), 5.40 (s, 1 H, H-1'), 4.88 (s, 1 H, H-1), 4.87 (d, 1 H, *J* = 10.5 Hz, $PhCH_2$), 4.78 (d,

2 H, J = 5.2 Hz, H-6' × 2), 4.74 (d, 1 H, J = 11.5 Hz, $PhCH_2$), 4.68 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.62 (d, 1 H, J = 11.5 Hz, $PhCH_2$), 4.56 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.50 (d, 1 H, J = 10.5 Hz, $PhCH_2$), 4.36 (s, 1 H, H-2), 4.27 (d, 1 H, J = 5.2 Hz, H-4'), 3.92-3.86 (m, 2 H, H-3, H-4), 3.83 (d, 1 H, J = 2.9 Hz, H-2'), 3.81-3.79 (m, 3 H, H-5, H-6 × 2), 3.76 (d, 1 H, J = 2.9 Hz, H-3'), 3.28 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.02 (C=O), 165.87 (C=O), 138.56 (Ar), 138.52 (Ar), 138.33 (Ar), 133.16 (Ar), 129.87 (Ar), 129.71 (Ar), 129.67 (Ar), 128.42 (Ar), 128.39 (Ar), 128.35 (Ar), 128.29 (Ar), 128.25 (Ar), 127.88 (Ar), 127.78 (Ar), 127.74 (Ar), 127.48 (Ar), 127.40 (Ar), 100.68 (C-1'), 100.08 (C-1), 79.21 (C-3), 75.06 ($PhCH_2$), 74.74 (C-4'), 74.69 (C-4), 73.41 ($PhCH_2$), 72.01 (C-2), 71.61 (C-5), 71.60 ($PhCH_2$), 71.52 (C-5'), 69.36 (C-6), 63.36 (C-6'), 55.26 (C-3'), 54.82 (OCH_3), 54.47 (C-2'). HRMS (ESI) calcd. for (M+Na) $C_{48}H_{48}O_{12}Na$ 839.3038, found 839.3041.

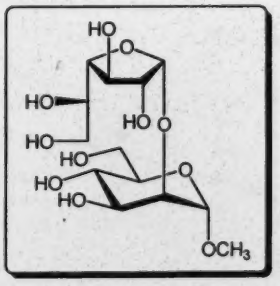
Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(3-*O*-benzyl-α-D-galactofuranosyl)-α-D-mannopyranoside (75).



Epoxide **50** (80 mg, 0.098 mmol) was opened following the general protocol, and the crude residue was purified by chromatography (1:2, hexanes:EtOAc) to yield **75** (41 mg, 55%) as colorless oil. R_f 0.33 (1:2, hexanes:EtOAc); $[\alpha]_D$ +18.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.18 (m, 20 H, Ar), 4.98 (d, 1 H, J = 4.8 Hz, H-1'), 4.96 (d, 1 H, J = 1.6 Hz, H-1), 4.89 (d, 1 H, J = 11.3

Hz, $PhCH_2$), 4.83 (d, 1 H, J = 10.9 Hz, $PhCH_2$), 4.69-4.55 (m, 5 H, $PhCH_2$), 4.52 (d, 1 H, J = 10.9 Hz, $PhCH_2$), 4.31 (dd, 1 H, J = 6.4, 4.8 Hz, H-2'), 4.19 (dd, 1 H, J = 6.4, 6.1, Hz, H-3'), 4.01 (dd, 1 H, J = 6.1, 3.7 Hz, H-4'), 3.96-3.92 (m, 1 H, H-3), 3.82-3.80 (m, 1 H, H-2), 3.80-3.76 (m, 2 H, H-4, H-5), 3.76-3.67 (m, 3 H, H-6 × 2, H-5'), 3.62-3.54 (m, 2 H, H-6' × 2), 3.36 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.17 (Ar), 138.13 (Ar), 137.96 (Ar), 137.68 (Ar), 128.55 (Ar), 128.42 (Ar), 128.37 (Ar), 128.02 (Ar), 127.99 (Ar), 127.86(Ar), 127.82 (Ar), 127.77 (Ar), 127.71 (Ar), 127.63 (Ar), 104.40 (C-1'), 99.05 (C-1), 83.47 (C-3'), 83.15 (C-4'), 78.95 (C-3), 78.56 (C-2'), 78.10 (C-2), 75.23 ($PhCH_2$), 74.97 (C-5), 73.38 ($PhCH_2$), 72.70 ($PhCH_2$), 72.11 ($PhCH_2$), 71.74 (C-5'), 71.39 (C-4), 68.96 (C-6), 64.47 (C-6'), 55.15 (OCH_3); HRMS (ESI) calcd. for (M+Na) $C_{41}H_{48}O_{11}Na$ 739.3089, found 739.3081.

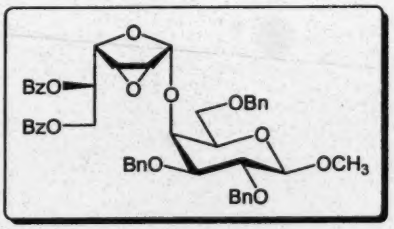
Methyl 2-*O*-(α-D-galactofuranosyl)-α-D-mannopyranoside (65).



To a solution of compound **75** (10 mg, 0.014 mmol) in CH_3OH (2 mL) was added 10% Pd/C (3 mg) and the reaction mixture was stirred under hydrogen atmosphere for 12 h. The mixture was filtered through Celite, and concentrated to yield compound **65** (5 mg, 100%) as a white foam. R_f 0.25 (4:1, CH_2Cl_2:CH_3OH); $[\alpha]_D$ +53.7 (*c* 0.5, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 5.07 (d, 1 H, J = 1.7 Hz, H-1), 4.99 (d, 1 H, J = 4.7 Hz, H-1'), 4.19 (dd, 1 H, J = 8.6, 7.5 Hz, H-3'), 3.95 (dd, 1 H, J = 8.6, 4.7 Hz, H-2'), 3.86 (dd, 1 H, J = 12.0, 1.8 Hz, H-6), 3.77 (dd, 1 H, J = 3.4, 1.7 Hz, H-2), 3.74

(dd, 1 H, J = 7.5, 3.1 Hz, H-4'), 3.74-3.67 (m, 2 H, H-3, H-6), 3.64-3.58 (m, 1 H, H-6'), 3.58-3.52 (m, 4 H, H-5', H-4, H-6', H-5), 3.39 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 104.74 (C-1'), 100.98 (C-1), 83.39 (C-4'), 81.85 (C-2), 78.86 (C-2'), 75.21 (C-3'), 75.02 (C-5), 72.84 (C-3), 72.04 (C-5'), 69.16 (C-4), 64.78 (C-6'), 62.83 (C-6), 55.62 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{13}H_{24}O_{11}Na$ 379.1211, found 379.1210.

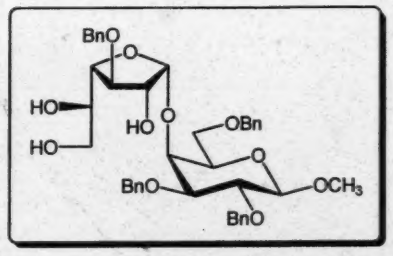
Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-anhydro-5,6-di-*O*-benzoyl-α-D-gulofuranosyl)-β-D-galactopyranoside (51).



The glycosylation of sulfoxide **6** (241 mg, 0.49 mmol) and sugar alcohol **35**[129] (216 mg, 0.46 mmol) was carried out following the general protocol, and after work-up, the crude reaction mixture was purified by chromatography (3:1, hexanes: EtOAc) to yield **51** (275 mg, 72%) as a white foam. R_f 0.34 (2:1, hexanes:EtOAc); $[\alpha]_D$ +23.7 (c 1.3, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.09-7.99 (m, 4 H, Ar), 7.59-7.54 (m, 2 H, Ar), 7.46-7.18 (m, 19 H, Ar), 5.74 (ddd, 1 H, J = 6.6, 5.0, 3.8 Hz, H-5'), 5.24 (s, 1 H, H-1'), 4.92 (d, 1 H, J = 10.9 Hz, $PhCH_2$), 4.75 (dd, 1 H, J = 12.3, 6.6 Hz, H-6'), 4.74 (d, 1 H, J = 10.9 Hz, $PhCH_2$), 4.69 (dd, 1 H, J = 12.3, 3.8 Hz, H-6'), 4.67 (d, 1 H, J = 11.2 Hz, $PhCH_2$), 4.58 (d, 1 H, J = 11.2 Hz, $PhCH_2$), 4.57 (d, 1 H, J = 3.2 Hz, H-4), 4.49 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.44 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.30 (d, 1 H, J = 7.7 Hz, H-1), 4.11 (d, 1 H, J = 5.0 Hz, H-4'), 3.80 (dd, 1 H, J = 10.7, 4.2 Hz, H-6), 3.74-3.66 (m, 2 H, H-2, H-6), 3.69 (d, 1 H, J

= 3.0 Hz, H-3'), 3.58 (s, 3 H, OCH_3), 3.59-3.56 (m, 1 H, H-5), 3.51 (d, 1 H, *J* = 3.0 Hz, H-2'), 3.40 (dd, 1 H, *J* = 9.7, 3.2 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.04 (C=O), 165.82 (C=O), 138.89 (Ar), 138.43 (Ar), 138.35 (Ar), 133.31 (Ar), 133.16 (Ar), 129.83 (Ar), 129.71 (Ar), 128.47 (Ar), 128.42 (Ar), 128.32 (Ar), 128.26 (Ar), 128.19 (Ar), 128.15 (Ar), 127.98 (Ar), 127.61 (Ar), 127.49 (Ar), 127.46 (Ar), 127.45 (Ar), 104.76 (C-1), 99.99 (C-1'), 80.66 (C-3), 79.75 (C-2), 75.16 ($PhCH_2$), 73.83 (C-5), 73.59 ($PhCH_2$), 73.45 (C-4'), 73.40 ($PhCH_2$), 71.24 (C-5'), 70.53 (C-6), 70.11 (C-4), 63.22 (C-6'), 56.95 (OCH_3), 55.35 (C-2'), 53.28 (C-3'). HRMS (ESI) calcd. for (M+Na) $C_{48}H_{48}O_{12}Na$ 839.3038, found 839.3038.

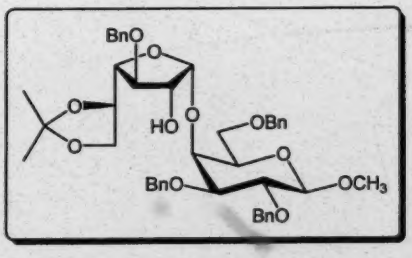
Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(3-*O*-benzyl-α-D-galactofuranosyl)-β-D-galactopyranoside (77).



Disaccharide **51** (404 mg, 0.49 mmol) was subjected to the general protocol to open the epoxide ring, and the crude residue was purified by chromatography (3:1, hexanes:EtOAc) to give **77** (207 mg, 69%) as a colorless oil. R_f 0.55 (1:1, hexanes:EtOAc); $[\alpha]_D$ +29.4 (*c* 1.5, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$, δ_H) 7.42-7.25 (m, 20 H, Ar), 4.97 (d, 1 H, *J* = 5.0 Hz, H-1'), 4.93 (d, 1 H, *J* = 11.4 Hz, $PhCH_2$), 4.90 (dd, 1 H, *J* = 10.9 Hz, $PhCH_2$), 4.86 (d, 1 H, *J* = 10.9 Hz, $PhCH_2$), 4.78 (d, 1 H, *J* = 12.5, $PhCH_2$), 4.76 (d, 1 H, *J* = 12.5 Hz, $PhCH_2$), 4.65 (d, 1 H, *J* = 11.4 Hz, $PhCH_2$), 4.54 (d, 1 H, *J* = 11.8 Hz, $PhCH_2$), 4.51 (d, 1 H, *J* = 11.8 Hz,

$PhCH_2$), 4.25 (d, 1 H, J = 7.6 Hz, H-1), 4.24 (dd, 1 H, J = 7.6, 7.5 Hz, H-3'), 4.18-4.15 (m, 1 H, H-2'), 4.13 (d, 1 H, J = 11.5 Hz, OH), 4.08 (d, 1 H, J = 3.0 Hz, H-4), 3.88 (dd, 1 H, J = 7.5, 1.5 Hz, H-4'), 3.70 (dd, 1 H, J = 9.2, 9.1 Hz, H-6), 3.68 (dd, 1 H, J = 9.9, 7.6 Hz, H-2), 3.59 (dd, 1 H, J = 9.2, 5.4 Hz, H-6), 3.59-3.55 (m, 1 H, H-5'), 3.53 (s, 3 H, OCH_3), 3.50 (dd, 1 H, J = 9.1, 5.4 Hz, H-5), 3.47 (dd, 1 H, J = 9.9, 3.0 Hz, H-3), 3.43-3.32 (m, 2 H, H-6' × 2), 2.75 (d, 1 H, J = 10.5 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.51 (Ar), 138.11 (Ar), 137.31 (Ar), 137.15 (Ar), 128.59 (Ar), 128.53 (Ar), 128.43 (Ar), 128.35 (Ar), 128.17 (Ar), 128.14 (Ar), 127.99 (Ar), 127.95 (Ar), 127.76 (Ar), 127.65 (Ar), 105.09 (C-1), 103.59 (C-1'), 82.57 (C-3'), 81.37 (C-4'), 79.64 (C-2), 79.59 (C-3), 78.04 (C-2'), 75.59 (C-4), 75.43 ($PhCH_2$), 73.66 ($PhCH_2$), 72.94 ($PhCH_2$), 72.53 ($PhCH_2$), 72.31 (C-5), 70.81 (C-5'), 66.65 (C-6), 65.04 (C-6'), 57.33 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{41}H_{48}O_{11}Na$ 739.3089, found 739.3091.

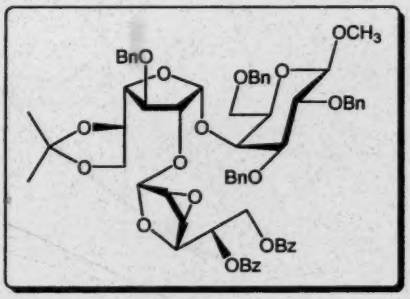
Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(3-*O*-benzyl-5,6-*O*-isopropylidene-α-D-galactofuranosyl)-β-D-galactopyranoside (78).



To a mixture of compound **77** (198 mg, 0.28 mmol) and 2,2-dimethoxypropane (0.27 mL, 2.2 mmol) in dry acetone (5 mL) was added cat. *p*-TsOH (2 mg) and the reaction mixture was stirred at room temperature for 4 h. 2 drops of triethylamine was added and the reaction mixture was concentrated. Column chromatography (3:1, hexanes:EtOAc) of the residue gave the

disaccharide **78** (0.185 g, 89%) as a colorless oil. R_f 0.38 (2:1, hexanes:EtOAc); $[\alpha]_D$ +45.9 (*c* 0.6, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.41-7.24 (m, 20 H, Ar), 5.19 (d, 1 H, *J* = 4.8 Hz, H-1'), 4.98 (d, 1 H, *J* = 13.3 Hz, $PhCH_2$), 4.91 (d, 1 H, *J* = 11.5 Hz, $PhCH_2$), 4.88 (d, 1 H, *J* = 11.1 Hz, $PhCH_2$), 4.80 (d, 1 H, *J* = 11.1, $PhCH_2$), 4.62 (d, 1 H, *J* = 13.3 Hz, $PhCH_2$), 4.59 (d, 1 H, *J* = 11.5 Hz, $PhCH_2$), 4.53 (s, 2 H, $PhCH_2$), 4.36 (ddd, 1 H, *J* = 8.0, 7.0, 7.0 Hz, H-5'), 4.27 (d, 1 H, *J* = 3.0 Hz, H-4), 4.24 (d, 1 H, *J* = 7.5 Hz, H-1), 4.17 (dd, 1 H, *J* = 6.8, 4.8 Hz, H-2'), 3.90 (dd, 1 H, *J* = 8.0, 7.0 Hz, H-4'), 3.84-3.74 (m, 2 H, H-6' × 2), 3.74 (dd, 1 H, *J* = 7.0, 6.8 Hz, H-3'), 3.68-3.59 (m, 2 H, H-6 × 2), 3.57 (dd, 1 H, *J* = 9.8, 7.5 Hz, H-2), 3.54 (s, 3 H, OCH_3), 3.49 (dd, 1 H, *J* = 8.7, 5.5 Hz, H-5), 3.43 (dd, 1 H, *J* = 9.8, 3.0 Hz, H-3), 1.39 (s, 3 H, isopropylidene CH_3), 1.21 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.60 (Ar), 138.48 (Ar), 137.71 (Ar), 137.21 (Ar), 128.59 (Ar), 128.45 (Ar), 128.21 (Ar), 128.16 (Ar), 128.11 (Ar), 128.02 (Ar), 127.86 (Ar), 127.58 (Ar), 127.56 (Ar), 127.31 (Ar), 109.47 (isopropylidene C), 105.02 (C-1), 102.97 (C-1'), 83.34 (C-3'), 82.26 (C-4'), 78.81 (C-3), 78.69 (C-2), 78.33 (C-2'), 78.30 (C-5'), 74.98 ($PhCH_2$), 73.69 ($PhCH_2$), 72.41 (C-5), 72.12 (C-4), 71.89 ($PhCH_2$), 70.45 ($PhCH_2$), 67.02 (C-6), 65.02 (C-6'), 57.23 (OCH_3), 26.69 (isopropylidene CH_3), 25.31 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{44}H_{52}O_{11}Na$ 779.3402, found 779.3404.

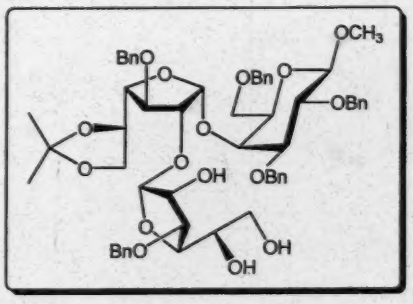
Methyl 2,3,6-tri-*O*-benzyl-4-*O*-[3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-(2,3-anhydro-5,6-di-*O*-benzoyl-α-D-gulofuranosyl)-α-D-galactofuranosyl]-β-D-galactopyranoside (79).



The glycosylation of disaccharide **78** (283 mg, 0.37 mmol) and donor **6** (553 mg, 1.12 mmol) was carried out following the general protocol, and after work-up, the crude residue was purified by column chromatography (2:1, hexanes:EtOAc) to yield compound **79** (243 mg, 59%) as a white foam. R_f 0.30 (3:2, hexanes:EtOAc); $[\alpha]_D$ +48.6 (*c* 0.51, CH_2Cl_2); ^{1}H NMR (600 MHz, CD_2Cl_2, δ_H) 8.04-7.97 (m, 4 H, Ar), 7.58-7.54 (m, 2 H, Ar), 7.45- 7.38 (m, 6 H, Ar), 7.35-7.20 (m, 18 H, Ar), 5.75 (ddd, 1 H, *J* = 6.4, 5.2, 4.0 Hz, H-5"), 5.14 (d, 1 H, *J* = 4.3 Hz, H-1'), 5.06 (s, 1 H, H-1"), 4.92 (d, 1 H, *J* = 12.8 Hz, $PhCH_2$), 4.82 (d, 1 H, *J* = 11.4 Hz, $PhCH_2$), 4.81 (d, 1 H, *J* = 10.8 Hz, $PhCH_2$), 4.76 (d, 1 H, *J* = 10.8 Hz, $PhCH_2$), 4.76-4.70 (m, 2 H, H-6" × 2), 4.61 (d, 1 H, *J* = 12.8 Hz, $PhCH_2$), 4.57 (d, 1 H, *J* = 11.4 Hz, $PhCH_2$), 4.56 (d, 1 H, *J* = 12.1 Hz, $PhCH_2$), 4.49 (d, 1 H, *J* = 12.1 Hz, $PhCH_2$), 4.44 (dd, 1 H, *J* = 6.6, 4.3 Hz, H-2'), 4.35 (ddd, 1 H, *J* = 6.8, 6.8, 6.8 Hz, H-5'), 4.24 (d, 1 H, *J* = 7.6 Hz, H-1), 4.19 (dd, 1 H, *J* = 5.2, 0.9 Hz, H-4"), 4.12 (d, 1 H, *J* = 3.0 Hz, H-4), 4.00 (dd, 1 H, *J* = 6.7, 6.6 Hz, H-3'), 3.82-3.79 (m, 2 H, H-6', H-3"), 3.76-3.73 (m, 2 H, H-6', H-4'), 3.69 (d, 1 H, *J* = 3.1 Hz, H-2"), 3.66-3.63 (m, 3 H, H-2, H-6 × 2), 3.52 (s, 3 H, OCH_3), 3.52-3.50 (m, 1 H, H-5), 3.40 (dd, 1 H, *J* = 9.8, 3.0 Hz, H-3), 1.34 (s, 3 H, isopropylidene CH_3), 1.20 (s, 3 H, isopropylidene CH_3); ^{13}C NMR

(125 MHz, CD_2Cl_2, δ_C) 166.32 (C=O), 166.07 (C=O), 139.58 (Ar), 139.33 (Ar), 138.60 (Ar), 138.40 (Ar), 133.66 (Ar), 133.55 (Ar), 130.17 (Ar), 130.10 (Ar), 129.97 (Ar), 128.87 (Ar), 128.83 (Ar), 128.81 (Ar), 128.64 (Ar), 128.55 (Ar), 128.48 (Ar), 128.33 (Ar), 128.24 (Ar), 128.17 (Ar), 128.08 (Ar), 128.02 (Ar), 127.71 (Ar), 127.56 (Ar), 109.60 (isopropylidene C), 105.39 (C-1), 102.51 (C-1'), 100.98 (C-1"), 82.16 (C-2'), 81.54 (C-3'), 81.52 (C-4'), 80.45 (C-3), 79.42 (C-2), 78.62 (C-5'), 75.51 (C-4"), 75.29 (Ph$\underline{C}H_2$), 73.74 (Ph$\underline{C}H_2$), 73.58 (C-4), 73.55 (C-5), 72.44 (Ph$\underline{C}H_2$), 71.82 (C-5"), 71.67 (Ph$\underline{C}H_2$), 69.15 (C-6), 65.44 (C-6'), 63.69 (C-6"), 57.25 (OCH_3), 55.67 (C-2"), 54.40 (C-3"), 26.96 (isopropylidene CH_3), 25.55 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{64}H_{68}O_{17}Na$ 1131.4354, found 1131.4351.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-[3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-(3-*O*-benzyl-α-D-galactofuranosyl)-α-D-galactofuranosyl]-β-D-galactopyranoside (80).



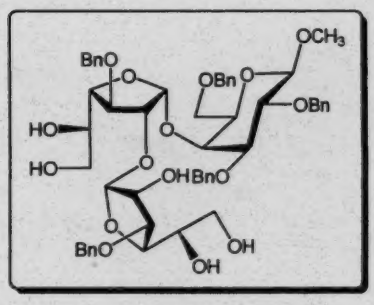
Compound **79** (110 mg, 0.1 mmol) was subjected to the general protocol to open the epoxide, and after work-up, the crude residue was purified by column chromatography (1:1, hexanes:EtOAc) to give **80** (61 mg, 61%) as a colorless syrup. R_f 0.29 (1:1, hexanes:EtOAc); $[\alpha]_D$ +57.0 (*c* 0.58, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.42-7.26 (m, 25 H, Ar), 5.16 (d, 1 H, J = 4.2 Hz, H-1'), 4.96 (d, 1 H, J = 4.9 Hz, H-1"), 4.90-4.86 (m, 3 H, $PhCH_2$ × 1.5), 4.82 (d, 1 H, J = 11.4 Hz, $PhCH_2$), 4.65 (d, 1 H, J = 11.4 Hz,

$PhCH_2$), 4.63-4.58 (m, 4 H, $PhCH_2$), 4.46 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.32 (d, 1 H, J = 3.0 Hz, H-4), 4.27 (d, 1 H, J = 7.6 Hz, H-1), 4.24-4.19 (m, 2 H, H-2", H-5'), 4.14-4.06 (m, 3 H, H-3', H-3", H-2'), 3.97 (dd, 1 H, J = 6.0, 4.8 Hz, H-4'), 3.94-3.89 (m, 2 H, H-6', H-4"), 3.77 (dd, 1 H, J = 9.2, 7.0 Hz, H-6'), 3.71 (dd, 1 H, J = 9.8, 7.6 Hz, H-2), 3.69-3.65 (m, 1 H, H-5"), 3.59-3.49 (m, 5 H, H-6" × 2, H-6 × 2, H-5), 3.33 (s, 3 H, OCH_3), 3.44 (dd, 1 H, J = 9.8, 3.0 Hz, H-3), 2.84 (br, 1 H, OH), 1.39 (s, 3 H, isopropylidene CH_3), 1.16 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.77 (Ar), 138.40 (Ar), 137.90 (Ar), 137.56 (Ar), 137.10 (Ar), 128.62 (Ar), 128.56 (Ar), 128.50 (Ar), 128.43 (Ar), 128.25 (Ar), 128.13 (Ar), 127.93 (Ar), 127.82 (Ar), 127.74 (Ar), 127.54 (Ar), 127.48 (Ar), 109.20 (isopropylidene C), 105.01 (C-1), 102.99 (C-1"), 101.19 (C-1'), 82.91 (C-3"), 82.66 (C-2'), 82.13 (C-4"), 82.02 (C-4'), 81.90 (C-3'), 79.78 (C-3), 79.03 (C-2), 77.72 (C-2"), 76.46 (C-5'), 75.28 ($PhCH_2$), 73.78 ($PhCH_2$), 72.44 (C-5), 72.27 (C-5"), 72.07 ($PhCH_2$), 71.77 ($PhCH_2$), 71.32 (C-4), 71.23 ($PhCH_2$), 67.18 (C-6), 65.08 (C-6'), 64.17 (C-6"), 57.20 (OCH_3), 26.36 (isopropylidene CH_3), 24.51 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{57}H_{68}O_{16}Na$ 1031.4405, found 1031.4407.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-[3-*O*-benzyl-2-*O*-(3-*O*-benzyl-α-D-galactofuranosyl)-α-D-galactofuranosyl]-β-D-galactopyranoside (81).

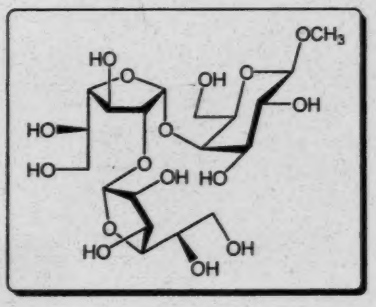
A solution of compound **80** (49 mg, 0.049 mmol) in 50 % HOAc (HOAc:H_2O:THF 5:3:2) was stirred at 50 °C for 12 h. The reaction mixture was concentrated and the resulting

residue was purified by chromatography (1:1, hexanes: EtOAc) to give **81** (38 mg, 81%) as a colorless syrup. R_f 0.4 (1:3, hexanes:EtOAc); $[\alpha]_D$ +50.7 (*c* 0.4, CH_3OH); ^1H NMR (600 MHz, CD_3OD, δ_H) 7.40-7.25 (m, 25 H, Ar), 5.12 (d, 2 H, J = 4.4 Hz, H-1', H-1"), 4.86-4.82 (m, 4 H, $PhCH_2$), 4.73 (d, 1 H, J = 11.1 Hz, $PhCH_2$), 4.71 (d, 1 H, J = 12.5 Hz, $PhCH_2$), 4.65 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.64 (d, 1 H, J = 11.1 Hz, $PhCH_2$), 4.59 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.54 (d, 1 H, J = 11.1 Hz, $PhCH_2$), 4.53 (dd, 1 H, J = 6.8, 6.4 Hz, H-3"), 4.27 (dd, 1 H, J = 6.8, 4.4 Hz, H-2"), 4.26 (d, 1 H, J = 7.7 Hz, H-1), 4.20 (dd, 1 H, J = 6.6, 4.4 Hz, H-2'), 4.12 (dd, 1 H, J = 6.6, 6.4 Hz, H-3'), 4.07 (d, 1 H, J = 3.0 Hz, H-4), 4.02 (dd, 1 H, J = 6.4, 2.5 Hz, H-4"), 3.90 (dd, 1 H, J = 6.4, 6.0 Hz, H-4'), 3.84 (dd, 1 H, J = 9.3, 7.7 Hz, H-6), 3.77 (ddd, 1 H, J = 6.3, 6.1, 6.0 Hz, H-5'), 3.65-3.58 (m, 3 H, H-2, H-6, H-5), 3.57-3.52 (m, 3 H, H-3, H-6', H-5"), 3.48 (s, 3 H, OCH_3), 3.43 (dd, 1 H, J = 11.5, 6.3 Hz, H-6'), 3.40-3.34 (m, 2 H, H-6" × 2); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 140.27 (Ar), 139.77 (Ar), 139.57 (Ar), 139.49 (Ar), 138.97 (Ar), 129.53 (Ar), 129.44 (Ar), 129.36 (Ar), 129.34 (Ar), 129.23 (Ar), 129.21 (Ar), 129.15 (Ar), 129.12 (Ar), 129.05 (Ar), 129.02 (Ar), 129.01 (Ar), 128.96 (Ar), 128.94 (Ar), 128.72 (Ar), 128.53 (Ar), 106.15 (C-1), 104.07 (C-1"), 102.95 (C-1'), 83.93 (C-3'), 82.65 (C-4'), 82.30 (C-2"), 81.99 (C-3"), 81.92 (C-4"), 81.29 (C-3), 80.82 (C-2), 78.82 (C-2'), 77.28 (C-4), 76.34 ($PhCH_2$), 74.35 ($PhCH_2$), 74.31 (C-5'), 73.93 (C-5), 73.92 ($PhCH_2$), 73.58 ($PhCH_2$),



73.02 (Ph$\underline{C}H_2$), 72.94 (C-5"), 68.69 (C-6), 64.23 (C-6', C-6"), 57.57 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{54}H_{64}O_{16}Na$ 991.4087, found 991.4088.

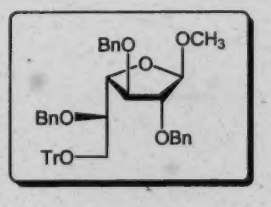
Methyl 4-*O*-[2-*O*-(α-D-galactofuranosyl)-α-D-galactofuranosyl]-β-D-galactopyranoside (66).



To a solution of compound **81** (12 mg, 0.012 mmol) in CH_3OH (2 mL) was added 10% Pd/C (3 mg) and the reaction mixture was stirred under hydrogen atmosphere for 12 h. The mixture was filtered through Celite and concentrated to yield compound **66** (6.5 mg, 100%) as a white foam. R_f 0.53 (1:4, CH_2Cl_2:CH_3OH); $[\alpha]_D$ +56.5 (*c* 0.54, CH_3OH); ^1H NMR (600 MHz, CD_3OD, δ_H) 5.03 (d, 1 H, *J* = 4.7 Hz, H-1'), 5.01 (d, 1 H, *J* = 4.8 Hz, H-1"), 4.43 (dd, 1 H, *J* = 8.9, 8.3 Hz, H-3"), 4.24 (dd, 1 H, *J* = 8.5, 7.8 Hz, H-3'), 4.14 (d, 1 H, *J* = 7.6 Hz, H-1), 4.06 (dd, 1 H, *J* = 8.9, 4.8 Hz, H-2"), 3.95 (dd, 1 H, *J* = 8.5, 4.7 Hz, H-2'), 3.90 (d, 1 H, *J* = 2.1 Hz, H-4), 3.82 (dd, 1 H, *J* = 10.8, 8.0 Hz, H-6), 3.79 (d, 1 H, *J* = 8.3 Hz, H-4"), 3.78 (dd, 1 H, *J* = 7.8, 3.5 Hz, H-4'), 3.73-3.69 (m, 1 H, H-5'), 3.69 (dd, 1 H, *J* = 10.8, 5.9 Hz, H-6), 3.65-3.56 (m, 5 H, H-6' × 2, H-6" × 2, H-5"), 3.53 (dd, 1 H, *J* = 8.1, 5.8 Hz, H-5), 3.51 (s, 3 H, OCH_3), 3.45-3.44 (m, 2 H, H-2, H-3); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 106.21 (C-1), 103.11 (C-1"), 102.26 (C-1'), 84.17 (C-2"), 82.63 (C-4'), 81.58 (C-4"), 79.43 (C-4), 79.06 (C-2'), 76.14 (C-5), 75.41 (C-3'), 74.27 (C-2), 72.90 (C-3"), 72.72 (C-5'), 72.45 (C-3), 71.52 (C-5"), 64.34 (C-6"), 64.24 (C-6'), 60.57

(C-6), 57.54 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{19}H_{34}O_{16}Na$ 541.1739, found 541.1739.

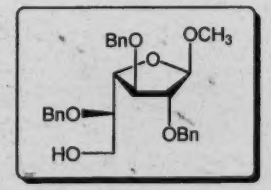
Methyl 2,3,5-tri-*O*-benzyl-6-*O*-trityl-β-D-galactofuranoside (85).



To a solution of **8** (2.5 g, 6.9 mmol) in methanol (10 mL) and CH_2Cl_2 (10 mL) was added $NaOCH_3$ until pH value was around 10. The mixture was allowed to stir for 12 h, neutralized by Amberlite IR-120 H^+ resin, filtered, and the filtrate was concentrated. The resulting crude residue was dissolved in pyridine (10 mL), followed by the addition of trityl chloride (2.3 g, 8.3 mmol) and DMAP (0.17 g, 1.4 mmol). The reaction mixture was stirred at 50 °C for 6 h and the TLC monitoring showed one major spot at R_f 0.59 (100% EtOAc). DMF (30 mL) was added to the mixture, followed by the addition of NaH (1.24 g, 31 mmol) and BnBr (3.0 mL, 24.8 mmol) at 0 °C. The resulting mixture was then stirred for 12 h at room temperature. The reaction was quenched by the addition of a few drops of methanol, diluted with CH_2Cl_2 (60 mL), and washed with a sat. aq. $NaHCO_3$ soln. (3 × 40 mL). The organic layer was subsequently dried (Na_2SO_4), concentrated and the residue was purified by chromatography (8:1, hexanes: EtOAc) to give **85** (3.71 g, 76%) as a light yellow oil. R_f 0.29 (8:1, hexanes: EtOAc); $[\alpha]_D$ –39.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.50-7.21 (m, 30 H, Ar), 4.94 (s, 1 H, H-1), 4.74 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.53 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.52 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.44 (d, 2 H, J = 11.8 Hz, $PhCH_2$), 4.29 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.19 (dd, 1 H, J = 7.2, 3.5 Hz, H-4),

3.98-3.95 (m, 2 H, H-2, H-3), 3.74-3.70 (m, 1 H, H-5), 3.46 (dd, 1 H, J = 9.9, 6.6 Hz, H-6), 3.38 (dd, 1 H, J = 9.9, 5.3 Hz, H-6), 3.34 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 144.11 (Ar × 3), 138.47 (Ar), 137.97 (Ar), 137.75 (Ar), 129.19 (Ar), 128.81 (Ar), 128.40 (Ar), 128.33 (Ar), 128.29 (Ar), 127.97 (Ar), 127.86 (Ar), 127.82 (Ar), 127.77 (Ar), 127.72 (Ar), 127.63 (Ar), 126.99 (Ar), 106.92 (C-1), 88.48 (C-2), 87.03 (trityl C), 83.03 (C-3), 81.18 (C-4), 77.01 (C-5), 73.37 ($PhCH_2$), 72.17($PhCH_2$), 71.83 ($PhCH_2$), 63.87 (C-6), 54.73 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{47}H_{46}O_6Na$ 729.3187, found 729.3184.

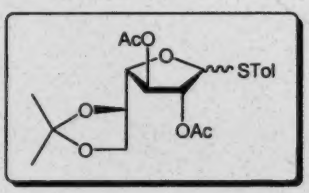
Methyl 2,3,5-tri-*O*-benzyl-β-D-galactofuranoside (82).



To a solution of compound **85** (0.89 g, 1.3 mmol) in CH_3OH (5 mL) and CH_2Cl_2 (20 mL) was added small crystals of *p*-TsOH until the pH value of the solution was around 3-4. The reaction mixture was stirred for 12 h at room temperature. Triethylamine was added to neutralize the reaction mixture, and the concentrated residue was purified by chromatography (3:1, hexanes:EtOAc) to provide **82** (0.50 g, 85%). R_f 0.25 (2:1, hexanes:EtOAc); $[\alpha]_D$ –47.4 (*c* 0.22, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.25 (m, 15 H, Ar), 4.97 (s, 1 H, H-1), 4.70 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.65 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.57 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.54 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.49 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.44 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.22 (dd, 1 H, J = 6.8, 5.1 Hz, H-4), 4.04 (dd, 1 H, J = 6.8, 2.8 Hz, H-3), 4.01-3.99 (m, 1 H, H-2), 3.79-3.65 (m, 3 H, H-6 × 2, H-5),

3.39 (s, 3 H, OCH_3), 2.24 (br, 1 H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.28 (Ar), 137.47 (Ar), 137.35 (Ar), 128.49 (Ar × 2), 128.41 (Ar × 4), 128.14 (Ar × 2), 128.03 (Ar × 2), 127.97 (Ar × 3), 127.91 (Ar), 127.76 (Ar), 107.05 (C-1), 87.81 (C-2), 83.12 (C-3), 82.19 (C-4), 78.27 (C-5), 72.77 ($PhCH_2$), 72.19 ($PhCH_2$), 72.04 ($PhCH_2$), 62.20 (C-6), 54.84 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{28}H_{32}O_6Na$ 487.2091, found 487.2093.

***p*-Tolyl 2,3-di-*O*-acetyl-5,6-*O*-isopropylidene-α/β-D-galactofuranoside (83).**



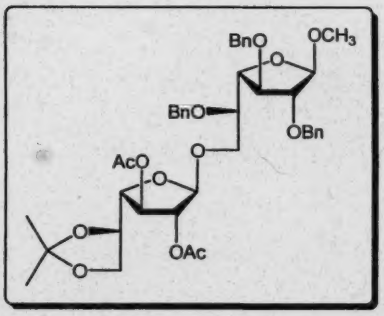
To a solution of an anomeric mixture of **10** and **11** (1.32 g, 4.6 mmol) and 2,2-dimethoxypropane (4.5 mL, 37 mmol) in acetone (30 mL) was added *p*-toluenesufonic acid (9 mg, cat.) at room temperature. The solution was allowed to stir for 4 h, and neutralized with a few drops of triethylamine. The mixture was concentrated and the resulting oil was dissolved in pyridine (7 mL), followed by the addition of acetic anhydride (1.3 mL, 14 mmol) at 0 °C. The reaction mixture was stirred for 6 h, diluted with CH_2Cl_2 (50 mL), and then washed with a sat. aq. $NaHCO_3$ soln. (3 × 30 mL). The organic layer was dried (Na_2SO_4), concentrated and the resulting residue was purified by chromatography (4:1, hexanes:EtOAc) to yield **83** (1.58 g, 84% over two steps) as a colorless oil. R_f 0.29 (3:1, hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.43-7.38 (m, 2 H, Ar), 7.13-7.10 (m, 2 H, Ar), 5.48 (d, 0.27 H, J = 4.7 Hz, H-1α), 5.45 (d, 0.73 H, J = 2.7 Hz, H-1β), 5.42 (dd, 0.27 H, J = 4.7, 2.9 Hz, H-2α), 5.23-5.21 (m, 1 H, H-2β, H-3α), 5.17 (dd, 0.73 H, J = 5.3, 2.4 Hz, H-3β), 4.46 (ddd, 0.27 H, J = 6.7, 6.6, 6.2 Hz, H-5α), 4.37 (ddd, 0.73 H, J = 6.8,

6.2, 4.8 Hz, H-5β), 4.29 (dd, 0.73 H, J = 5.3, 4.8 Hz, H-4β), 4.06 (dd, 0.27 H, J = 8.2, 6.7 Hz, H-6α), 4.04 (dd, 0.73 H, J = 8.4, 6.8 Hz, H-6β), 3.92 (dd, 0.27 H, J = 6.2, 4.4 Hz, H-4α), 3.89 (dd, 0.73 H, J = 8.4, 6.2 Hz, H-6β), 3.90-3.86 (dd, 0.27 H, J = 8.2, 6.6 Hz, H-6α), 2.32 (s, 3 H, tolyl CH_3), 2.15 (s, 0.81 H, acyl CH_3α), 2.11 (s, 2.19 H, acyl CH_3β), 2.08 (s, 2.19 H, acyl CH_3β), 2.07 (s, 0.81 H, acyl CH_3α), 1.46 (s, 0.81 H, isopropylidene CH_3α), 1.40 (s, 2.19 H, isopropylidene CH_3β), 1.38 (s, 0.81 H, isopropylidene CH_3α), 1.36 (s, 2.19 H, isopropylidene CH_3β); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.98 (C=Oβ), 169.62 (C=Oβ), 169.55 (C=Oα), 169.46 (C=Oα), 138.05 (Arβ), 137.92 (Arα), 132.90 (Arβ × 2), 132.59 (Arα × 2), 130.02 (Arα), 129.77 (Arβ × 2), 129.69 (Arα × 2), 129.55 (Arβ), 109.94 (isopropylidene Cα), 109.85 (isopropylidene Cβ), 91.01 (C-1β), 89.69 (C-1α), 83.40 (C-4α), 81.73 (C-4β), 81.31 (C-2β), 77.64 (C-2α), 77.22 (C-3α/β), 75.57 (C-5α), 75.57 (C-5β), 65.46 (C-6α), 65.39 (C-6β), 26.43 (isopropylidene CH_3α), 26.19 (isopropylidene CH_3β), 25.35 (isopropylidene CH_3β), 25.24 (isopropylidene CH_3α), 21.11 (tolyl CH_3α/β), 20.80 (acyl CH_3α/β), 20.74 (acyl CH_3β) 20.64 (acyl CH_3α). HRMS (ESI) calcd. for (M+Na) $C_{20}H_{26}O_7SNa$ 433.1292, found 433.1289.

Methyl 2,3,5-tri-*O*-benzyl-6-*O*-(2,3-di-*O*-acetyl-5,6-*O*-isopropylidene-β-D-galactofuranosyl)-β-D-galactofuranoside (89).

To a mixture of **82** (790 mg, 1.7 mmol), **83** (770 mg, 1.9 mmol) and 4 Å molecular sieves (0.5 g) in CH_2Cl_2 (50 mL) was added *N*-iodosuccinimide (534 mg, 2.25 mmol) followed by silver triflate (146 mg, 0.56 mmol) at 0 °C. After stirring for 20 min at 0 °C, the

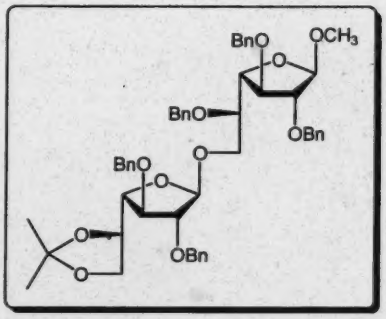
reaction mixture turned dark red, and triethylamine was added, which was then diluted with CH_2Cl_2 (50 mL) and filtered through Celite. The filtrate was washed with sat. aq. $Na_2S_2O_3$ soln. (3 × 50 mL), dried (Na_2SO_4), and concentrated to give a crude residue



that was purified by chromatography (3:1, hexanes:EtOAc) to give **89** (1.24 g, 94%) as a colorless oil. R_f 0.25 (2:1, hexanes:EtOAc); $[\alpha]_D$ –86.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.38-7.21 (m, 15 H, Ar), 5.08 (s, 1 H, H-1'), 5.06 (d, 1 H, *J* = 1.3 Hz, H-2'), 5.02 (dd, 1 H, *J* = 4.8, 1.3 Hz, H-3'), 4.95 (s, 1 H, H-1), 4.69 (d, 1 H, *J* = 11.7 Hz, $PhCH_2$), 4.56 (d, 1 H, *J* = 11.9 Hz, $PhCH_2$), 4.51 (d, 1 H, *J* = 11.7 Hz, $PhCH_2$), 4.47 (d, 1 H, *J* = 11.9 Hz, $PhCH_2$), 4.46 (d, 1 H, *J* = 11.7 Hz, $PhCH_2$), 4.33 (ddd, 1 H, *J* = 6.7, 6.1, 6.1 Hz, H-5'), 4.31 (d, 1 H, *J* = 11.7 Hz, $PhCH_2$), 4.12-4.08 (m, 2 H, H-4, H-4'), 4.04 (dd, 1 H, *J* = 8.6, 6.7 Hz, H-6'), 4.01 (dd, 1 H, *J* = 7.2, 3.3 Hz, H-3), 3.96-3.94 (m, 1 H, H-2), 3.94 (dd, 1 H, *J* = 10.1, 5.2 Hz, H-6), 3.85 (dd, 1 H, *J* = 8.6, 6.1 Hz, H-6'), 3.78-3.74 (m, 1 H, H-5), 3.67 (dd, 1 H, *J* = 10.1, 7.0 Hz, H-6), 3.35 (s, 3 H, OCH_3), 2.08 (s, 3 H, acyl CH_3), 2.06 (s, 3 H, acyl CH_3), 1.43 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.07 (C=O), 169.56 (C=O), 138.26 (Ar), 137.83 (Ar), 137.65 (Ar), 128.38 (Ar × 2), 128.33 (Ar × 2), 128.30 (Ar × 2), 128.27 (Ar × 2), 128.01 (Ar × 2), 127.85 (Ar × 2), 127.77 (Ar × 2), 127.67 (Ar), 109.89 (isopropylidene C), 107.17 (C-1), 105.62 (C-1'), 88.39 (C-2), 82.86 (C-4'), 82.62 (C-3), 81.29 (C-2'), 80.53 (C-4), 76.97 (C-3'), 75.88 (C-5), 75.32 (C-5'), 73.37 ($PhCH_2$), 72.13

(Ph$\underline{C}$H$_2$), 71.86 (Ph$\underline{C}$H$_2$), 67.32 (C-6), 65.49 (C-6'), 54.89 (OCH_3), 26.32 (isopropylidene CH_3), 25.23 (isopropylidene CH_3), 20.73 (acyl CH_3 × 2). HRMS (ESI) calcd. for (M+Na) $C_{41}H_{50}O_{13}Na$ 773.3144, found 773.3147.

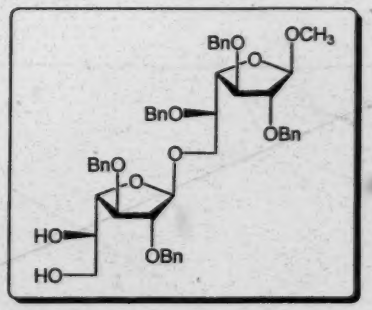
Methyl 2,3,5-tri-*O*-benzyl-6-*O*-(2,3-di-*O*-benzyl-5,6-*O*-isopropylidene-β-D-galactofuranosyl)-β-D-galactofuranoside (90).



To a solution of **89** (1.2 g, 1.6 mmol) in methanol (15 mL) and CH_2Cl_2 (15 mL) was added $NaOCH_3$ until pH value of the solution was around 10. The mixture was stirred for 12 h, neutralized by addition of acetic acid, and concentrated. The crude was dissolved in DMF (20 mL), followed by the addition of NaH (0.19 g, 4.8 mmol) and BnBr (0.5 mL, 4.0 mmol) at 0 °C. The reaction mixture was then stirred for 12 h at room temperature, quenched by addition of methanol, diluted with CH_2Cl_2 (50 mL), and washed with a sat. aq. $NaHCO_3$ soln. (3 × 30 mL). The organic layer was subsequently dried (Na_2SO_4), concentrated and the residue was purified by chromatography (8:1, hexanes: EtOAc) to give **90** (1.3 g, 76%) as a light yellow oil. R_f 0.29 (8:1, hexanes:EtOAc); $[\alpha]_D$ –63.2 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.39-7.23 (m, 25 H, Ar), 5.13 (s, 1 H, H-1'), 4.98 (s, 1 H, H-1), 4.78 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.60-4.54 (m, 3 H, $PhCH_2$), 4.51-4.44 (m, 5 H, $PhCH_2$), 4.33 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.22 (ddd, 1 H, J = 6.8, 6.8, 6.7 Hz, H-5'), 4.11-4.07 (m, 2 H, H-4, H-4'), 4.06-4.04 (m, 1 H, H-2'), 4.04 (dd, 1 H,

J = 7.2, 3.0 Hz, H-3), 4.00 (dd, 1 H, J = 10.4, 3.9 Hz, H-6), 4.00-3.98 (m, 1 H, H-2), 3.90 (dd, 1 H, J = 8.2, 6.7 Hz, H-6'), 3.87-3.80 (m, 3 H, H-6', H-5, H-3'), 3.75 (dd, 1 H, J = 10.4, 7.7 Hz, H-6), 3.37 (s, 3 H, OCH_3), 1.44 (s, 3 H, isopropylidene CH_3), 1.38 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.49 (Ar), 137.80 (Ar), 137.70 (Ar), 137.50 (Ar), 137.36 (Ar), 128.60 (Ar), 128.47 (Ar), 128.41 (Ar), 128.38 (Ar), 128.34 (Ar), 128.25 (Ar), 128.17 (Ar), 128.07 (Ar), 127.96 (Ar), 127.90 (Ar), 127.85 (Ar), 127.76 (Ar), 127.55 (Ar), 109.68 (isopropylidene C), 106.97 (C-1), 106.56 (C-1'), 88.33 (C-2), 87.87 (C-2'), 84.12 (C-3'), 82.90 (C-3), 81.97 (C-4'), 80.82 (C-4), 76.36 (C-5'), 76.21 (C-5), 73.60 ($PhCH_2$), 72.18 ($PhCH_2$ × 2), 71.98 ($PhCH_2$), 71.84 ($PhCH_2$), 68.91 (C-6), 65.40 (C-6'), 54.76 (OCH_3), 26.52 (isopropylidene CH_3), 25.39 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{51}H_{58}O_{11}Na$ 869.3871, found 869.3876.

Methyl 2,3,5-tri-*O*-benzyl-6-*O*-(2,3-di-*O*-benzyl-β-D-galactofuranosyl)-β-D-galacto-furanoside (91).

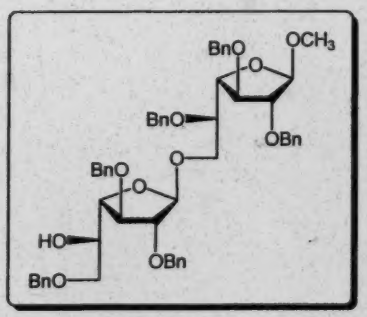


A solution of compound **90** (190 mg, 0.22 mmol) in 50% HOAc (6 mL, HOAc:H_2O:THF 3:2:1) was stirred for 10 h at 50 °C. The resulting mixture was concentrated and purified by chromatography (3:2, hexanes:EtOAc) to give **91** (153 mg, 85%) as a colorless syrup. R_f 0.25 (1:1, hexanes:EtOAc); $[\alpha]_D$ –67.5 (c 0.9, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40-7.25

(m, 25 H, Ar), 5.07 (s, 1 H, H-1'), 4.97 (s, 1 H, H-1), 4.73 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.61-4.45 (m, 8 H, $PhCH_2$ × 4), 4.34 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.14-4.10 (m, 2 H, H-4, H-4'), 4.08 (dd, 1 H, J = 6.6, 2.7 Hz, H-3'), 4.04-4.02 (m, 1 H, H-2'), 4.01 (dd, 1 H, J = 6.9, 3.0 Hz, H-3), 3.98 (d, 1 H, J = 3.0, H-2), 3.89 (dd, 1 H, J = 10.4, 4.1 Hz, H-6), 3.81-3.74 (m, 2 H, H-5, H-5'), 3.69 (dd, 1 H, J = 10.4, 7.5 Hz, H-6), 3.70-3.61 (m, 2 H, H-6' × 2), 3.38 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.37 (Ar), 137.76 (Ar), 137.63 (Ar), 137.55 (Ar), 137.19 (Ar), 128.51 (Ar), 128.48 (Ar), 128.42 (Ar), 128.37 (Ar), 128.29 (Ar), 128.14 (Ar), 128.08 (Ar), 128.02 (Ar), 127.94 (Ar), 127.87 (Ar), 127.83 (Ar), 127.81 (Ar), 127.63 (Ar), 107.07 (C-1), 106.92 (C-1'), 88.17 (C-2), 87.54 (C-2'), 83.56 (C-3'), 82.78 (C-3), 82.32 (C-4'), 80.88 (C-4), 76.54 (C-5), 73.52 ($PhCH_2$), 72.41 ($PhCH_2$), 72.13 ($PhCH_2$), 72.02 ($PhCH_2$), 71.90 ($PhCH_2$), 71.22 (C-5), 68.62 (C-6), 64.41 (C-6'), 54.88 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{48}H_{54}O_{11}Na$ 829.3558, found 829.3550.

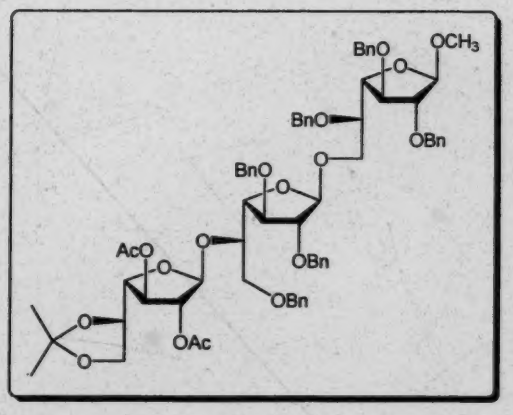
Methyl 2,3,5-tri-*O*-benzyl-6-*O*-(2,3,6-tri-*O*-benzyl-β-D-galactofuranosyl)-β-D-galacto -furanoside (92).

Compound **92** (500 mg, 0.62 mmol) and dibutyltin oxide (236 mg, 0.93 mmol) in dry toluene (15 mL) were heated under reflux for 6 h, and then Bu_4NBr (200 mg, 0.62 mmol) and benzyl bromide (90 μL, 0.74 mmol) were



introduced. The reaction mixture was heated under reflux for 24 h and then concentrated. The resulting residue was dissolved into ethyl acetate (30 mL), washed with 10% aq. KF soln. (30 mL) and brine (30 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated and the crude product was purified by column chromatography (3:1, hexanes:EtOAc) to give **92** (432 mg, 78%) as a colorless oil. R_f 0.32 (2:1, hexanes:EtOAc); $[\alpha]_D$ –53.5 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.38-7.22 (m, 30 H, Ar), 5.09 (br s, 1 H, H-1'), 4.94 (br s, 1 H, H-1), 4.73 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.58-4.43 (m, 10 H, $PhCH_2$ × 5), 4.32 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.13 (dd, 1 H, J = 6.4, 3.5 Hz, H-4'), 4.10-4.07 (m, 2 H, H-4, H-3'), 4.02 (dd, 1 H, J = 2.7, 1.0 Hz, H-2'), 4.01 (dd, 1 H, J = 7.0, 3.1 Hz, H-3), 3.96 (dd, 1 H, J = 3.1, 1.2 Hz, H-2), 3.92 (br, 1 H, H-5'), 3.91 (dd, 1 H, J = 10.4, 4.0 Hz, H-6), 3.79 (ddd, 1 H, J = 7.7, 4.0, 3.5 Hz, H-5), 3.68 (dd, 1 H, J = 10.4, 7.7 Hz, H-6), 3.56-3.51 (m, 2 H, H-6' × 2), 3.33 (s, 3 H, OCH_3), 2.40 (br, 1 H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.46 (Ar), 138.05 (Ar), 137.81 (Ar), 137.78 (Ar), 137.78 (Ar), 137.33 (Ar), 128.45 (Ar), 128.40 (Ar), 128.34 (Ar), 128.26 (Ar), 128.15 (Ar), 128.10 (Ar), 128.09 (Ar), 128.03 (Ar), 127.91 (Ar), 127.88 (Ar), 127.84 (Ar), 127.80 (Ar), 127.79 (Ar), 127.76 (Ar), 127.70 (Ar), 127.68 (Ar), 127.56 (Ar), 107.02 (C-1), 106.75 (C-1'), 88.28 (C-2), 87.59 (C-2'), 83.44 (C-3'), 82.84 (C-3), 81.63 (C-4'), 80.90 (C-4), 76.40 (C-5), 73.61 ($PhCH_2$), 73.39 ($PhCH_2$), 72.30 ($PhCH_2$), 72.14 ($PhCH_2$), 71.88 ($PhCH_2$), 71.84 ($PhCH_2$), 71.57 (C-6'), 70.14 (C-5'), 68.67 (C-6), 54.77 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{55}H_{60}O_{11}Na$ 919.4028, found 919.4022.

Methyl 2,3,5-tri-*O*-benzyl-6-*O*-[2,3,6-tri-*O*-benzyl-5-*O*-(2,3-di-*O*-acetyl-5,6-*O*-isopropylidene-β-D-galactofuranosyl)-β-D-galactofuranosyl]-β-D-galactofuranoside (93).



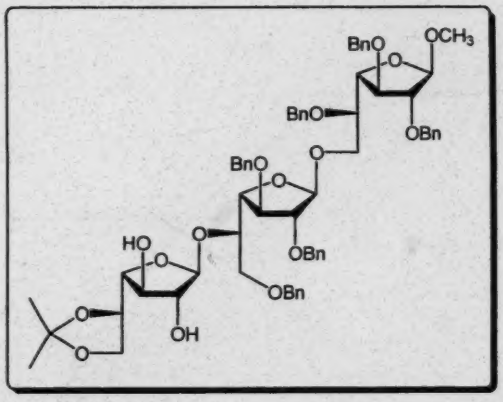
To a mixture of **83** (61 mg, 0.15 mmol), **92** (102 mg, 0.11 mmol) and 4 Å molecular sieves (0.2 g) in CH_2Cl_2 (6 mL) was added *N*-iodosuccinimide (42 mg, 0.18 mmol) followed by silver triflate (12 mg, 0.044 mmol) at 0 °C. After stirring for 20 min at 0 °C, the reaction mixture turned dark red, and triethylamine was added, which was then diluted with CH_2Cl_2 (20 mL) and filtered through Celite. The filtrate was washed with sat. aq. $Na_2S_2O_3$ soln. (3 × 10 mL), dried (Na_2SO_4), and concentrated to give a crude residue that was purified by chromatography (3:1, hexanes:EtOAc) to give **93** (119 mg, 89%) as a colorless syrup. R_f 0.31 (2:1, hexanes:EtOAc); $[\alpha]_D$ –57.8 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.38-7.21 (m, 30 H, Ar), 5.51 (s, 1 H, H-1"), 5.20 (d, 1 H, J = 1.2 Hz, H-2"), 5.09 (d, 1 H, J = 1.4 Hz, H-1'), 5.02 (dd, 1 H, J = 4.6, 1.2 Hz, H-3"), 4.94 (s, 1 H, H-1), 4.75 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.60-4.44 (m, 9 H, $PhCH_2$ × 4.5), 4.41 (d, 1 H, J = 11.5 Hz, $PhCH_2$), 4.31 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.25 (ddd, 1 H, J = 6.2, 6.2, 6.2 Hz, H-5"), 4.22-4.13 (m, 4 H, H-5', H-4", H-3', H-4'), 4.07 (dd, 1 H, J = 7.1, 3.0 Hz, H-4), 4.03 (dd, 1 H, J = 3.4, 1.4 Hz, H-2'), 4.01 (dd, 1 H, J = 7.1, 3.1 Hz, H-3), 3.97-3.92

(m, 2 H, H-2, H-6"), 3.90 (dd, 1 H, J = 10.1, 3.9 Hz, H-6), 3.81-3.77 (m, 2 H, H-6", H-5), 3.73 (dd, 1 H, J = 10.2, 7.5 Hz, H-6'), 3.71-3.67 (m, 1 H, H-6), 3.65 (dd, 1 H, J = 10.2, 4.2 Hz, H-6'), 3.35 (s, 3 H, OCH_3), 2.04 (s, 3 H, acyl CH_3), 1.92 (s, 3 H, acyl CH_3), 1.35 (s, 3 H, isopropylidene CH_3), 1.33 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.19 (C=O), 169.33 (C=O), 138.42 (Ar), 138.16 (Ar), 137.99 (Ar), 137.79 (Ar), 137.66 (Ar), 137.43 (Ar), 128.40 (Ar), 128.37 (Ar), 128.34 (Ar), 128.30 (Ar), 128.26 (Ar), 128.11 (Ar), 128.00 (Ar), 127.88 (Ar), 127.83 (Ar), 127.78 (Ar), 127.77 (Ar), 127.70 (Ar), 127.67 (Ar), 127.57 (Ar), 127.48 (Ar), 109.76 (isopropylidene C), 107.00 (C-1), 106.56 (C-1'), 105.45 (C-1"), 88.58 (C-2'), 88.26 (C-2), 83.52 (C-4'), 83.20 (C-4"), 82.85 (C-3), 81.23 (C-2"), 80.88 (C-4), 80.36 (C-3'), 76.97 (C-3"), 76.26 (C-5), 75.35 (C-5"), 73.60 (Ph$\underline{C}H_2$), 73.36 (Ph$\underline{C}H_2$), 73.17 (C-5'), 72.32 (Ph$\underline{C}H_2$), 72.15 (Ph$\underline{C}H_2$ × 2), 71.84 (Bn CH_2), 71.17 (C-6'), 68.75 (C-6), 65.42 (C-6"), 54.75 (OCH_3), 26.25 (isopropylidene CH_3), 25.23 (isopropylidene CH_3), 20.70 (acyl CH_3), 20.61 (acyl CH_3). HRMS (ESI) calcd. for (M+Na) $C_{68}H_{78}O_{18}Na$ 1205.5086, found 1205.5093.

Methyl 2,3,5-tri-*O*-benzyl-6-*O*-[2,3,6-tri-*O*-benzyl-5-*O*-(5,6-*O*-isopropylidene-β-D-galactofuranosyl)-β-D-galactofuranosyl]-β-D-galactofuranoside (94).

To a solution of **93** (635 mg, 0.54 mmol) in methanol (25 mL) and CH_2Cl_2 (25 mL) was added $NaOCH_3$ until pH value of the solution was around 10. The mixture was allowed to stir for 12 h, neutralized by addition of acetic acid, and concentrated. The crude residue was purified by chromatography (3:2, hexanes:EtOAc) to give **94** (535 mg, 91%) as a

colorless syrup. R_f 0.36 (1:1, hexanes: EtOAc); $[\alpha]_D$ –55.9 (*c* 1.1, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.38-7.21 (m, 30 H, Ar), 5.36 (s, 1 H, H-1"), 5.05 (s, 1 H, H-1'), 4.95 (s, 1 H, H-1), 4.73 (dd, 1 H, *J* = 11.8 Hz, $PhCH_2$), 4.58-4.44 (m, 8 H, $PhCH_2$ × 4), 4.38 (d, 1 H, *J* = 12.1 Hz, $PhCH_2$), 4.37 (d, 1 H, *J* = 11.9 Hz, $PhCH_2$), 4.33 (d, 1 H, *J* = 11.8 Hz, $PhCH_2$), 4.22 (dd, 1 H, *J* = 7.7, 6.9 Hz, H-5"), 4.16-4.09 (m, 2 H, H-4', H-5'), 4.08 (dd, 1 H, *J* = 7.0, 3.2 Hz, H-4), 4.04-3.84 (m, 10 H, H-3, H-4", H-3", H-2', H-2, H-2", H-6" × 2, H-3', H-6), 3.77 (ddd, 1 H, *J* = 7.7, 3.7, 3.2 Hz, H-5), 3.75 (br, 1 H, OH), 3.67 (dd, 1 H, *J* = 10.3, 7.7 Hz, H-6), 3.61 (dd, 1 H, *J* = 10.3, 4.0 Hz, H-6'), 3.57 (dd, 1 H, *J* = 10.3, 6.3 Hz, H-6'), 3.36 (s, 3 H, OCH_3), 1.40 (s, 3 H, isopropylidene CH_3), 1.38 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.49 (Ar), 137.91 (Ar), 137.84 (Ar), 137.69 (Ar), 137.50 (Ar), 137.12 (Ar), 128.51 (Ar), 128.40 (Ar), 128.33 (Ar), 128.24 (Ar), 128.12 (Ar), 128.10 (Ar), 128.00 (Ar), 127.85 (Ar), 127.81 (Ar), 127.77 (Ar), 127.73 (Ar), 127.68 (Ar), 127.61 (Ar), 127.54 (Ar), 109.99 (isopropylidene C), 107.14 (C-1"), 106.99 (C-1), 106.09 (C-1'), 88.26 (C-2"), 87.07 (C-2'), 85.35 (C-2), 84.56 (C-3'), 82.94 (C-4"), 81.43 (C-4'), 80.85 (C-4), 78.88 (C-3"), 78.57 (C-3), 76.38 (C-5), 75.87 (C-5"), 73.58 (C-5'), 73.52 ($PhCH_2$), 73.43 ($PhCH_2$), 72.13 ($PhCH_2$), 72.02 ($PhCH_2$), 71.89 ($PhCH_2$), 71.84 ($PhCH_2$), 69.94 (C-6'), 68.41 (C-6),



65.69 (C-6"), 54.77 (OCH_3), 25.71 (isopropylidene CH_3), 25.56 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{64}H_{74}O_{16}Na$ 1121.4874, found 1121.4877.

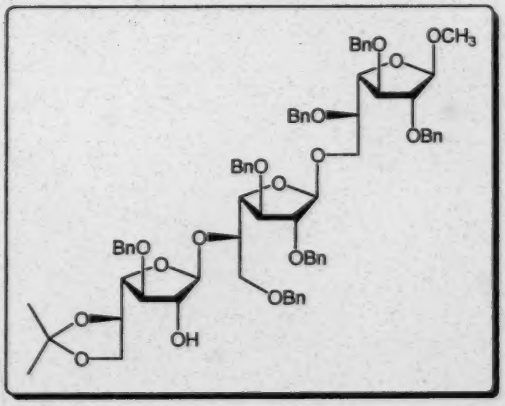
Methyl 2,3,5-tri-*O*-benzyl-6-*O*-[2,3,6-tri-*O*-benzyl-5-*O*-(2,3-anhydro-5,6-*O*-isopropyl -idene-β-D-gulofuranosyl)-β-D-galactofuranosyl]-β-D-galactofuranoside (95).

To a solution of **94** (535 mg, 0.487 mmol) and PPh_3 (383 mg, 1.46 mmol) in THF (25 mL) at 0 °C was added DIAD (0.30 mL, 1.46 mmol) dropwise. The reaction mixture was allowed to warm to room temperature over the course of 30 min, and then stirred for another 30 min at 40 °C. The resulting mixture was concentrated and the residue was purified by chromatography (3:1, hexanes:EtOAc) to yield **95** (481 mg, 91%) as a colorless syrup. R_f 0.65 (3:2, hexanes: EtOAc); $[\alpha]_D$ –53.6 (*c* 0.7, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.38-7.20 (m, 30 H, Ar), 5.47 (s, 1 H, H-1"), 5.13 (s, 1 H, H-1'), 4.94 (br s, 1 H, H-1), 4.74 (dd, 1 H, J = 11.8 Hz, $PhCH_2$), 4.64 (d, 1 H, J = 11.3 Hz, $PhCH_2$), 4.59-4.40 (m, 9 H, $PhCH_2$ × 4.5), 4.31 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.21 (ddd, 1 H, J = 6.8, 6.8, 6.8 Hz, H-5"), 4.17 (ddd, 1 H, J = 8.2, 3.8, 2.1 Hz, H-5'), 4.14 (d, 1 H, J = 7.2 Hz, H-3'), 4.13 (d, 1 H, J = 6.8 Hz, H-4"), 4.10-3.99 (m, 5 H, H-4, H-4', H-6", H-2', H-3), 3.96 (dd, 1 H, J = 3.1, 1.2 Hz, H-2), 3.88 (dd, 1 H, J = 10.4, 4.0 Hz, H-6), 3.79-3.70 (m, 3 H, H-5, H-6", H-6'), 3.71 (d, 1 H, J = 2.9 Hz, H-2"), 3.68 (dd, 1 H, J = 10.4, 7.7 Hz,

H-6), 3.60 (dd, 1 H, J = 10.1, 3.8 Hz, H-6'), 3.44 (d, 1 H, J = 2.9 Hz, H-3"), 3.32 (s, 3 H, OCH_3), 1.38 (s, 3 H, isopropylidene CH_3), 1.34 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.43 (Ar), 138.14 (Ar), 138.07 (Ar), 137.80 (Ar), 137.67 (Ar), 137.61 (Ar), 128.42 (Ar), 128.40 (Ar), 128.37 (Ar), 128.34 (Ar), 128.30 (Ar), 128.26 (Ar), 128.14 (Ar), 127.99 (Ar), 127.88 (Ar), 127.84 (Ar), 127.78 (Ar), 127.76 (Ar), 127.65 (Ar), 127.64 (Ar), 127.57 (Ar), 127.46 (Ar), 109.68 (isopropylidene C), 107.02 (C-1), 106.55 (C-1'), 102.00 (C-1"), 88.25 (C-2), 88.17 (C-2'), 84.31 (C-3'), 82.88 (C-3), 80.98 (C-4), 80.88 (C-4'), 77.26 (C-4"), 76.23 (C-5), 75.28 (C-5'), 75.14 (C-5"), 73.59 ($PhCH_2$), 73.35 ($PhCH_2$), 72.80 ($PhCH_2$), 72.16 ($PhCH_2$), 71.95 ($PhCH_2$), 71.84 ($PhCH_2$), 71.58 (C-6'), 68.62 (C-6), 65.63 (C-6"), 55.65 (C-2"), 54.75 (OCH_3), 53.65 (C-3"), 26.63 (isopropylidene CH_3), 25.17 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{64}H_{72}O_{15}Na$ 1103.4769, found 1103.4770.

Methyl 2,3,5-tri-*O*-benzyl-6-*O*-[2,3,6-tri-*O*-benzyl-5-*O*-(3-*O*-benzyl-5,6-*O*-isopropylidene-β-D-galactofuranosyl)-β-D-galactofuranosyl]-β-D-galactofuranoside (96).

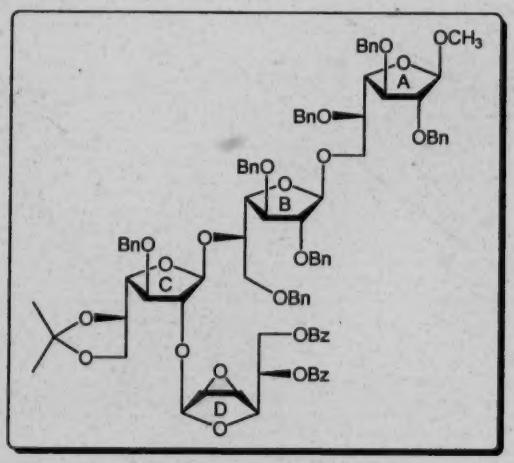
A prepared solution of lithium benzylate in benzyl alcohol (2 M, 8 mL) was added to compound **95** (481 mg, 0.445 mmol). The reaction mixture was heated to 75 °C and stirred for 12 h, followed by neutralization



with acetic acid. The resulting mixture was diluted with ethyl acetate (20 mL) and washed with water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give crude mixture, which was purified by column chromatography (3:1, hexanes:EtOAc) to yield **96** (458 mg, 87%) as a colorless oil. R_f 0.47 (2:1, hexanes:EtOAc); $[\alpha]_D$ –76.6 (*c* 0.4, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.37-7.20 (m, 35 H, Ar), 5.39 (s, 1 H, H-1"), 5.08 (d, 1 H, J = 1.6 Hz, H-1'), 4.94 (s, 1 H, H-1), 4.75 (dd, 1 H, J = 11.8 Hz, $PhCH_2$), 4.66 (d, 1 H, J = 12.3 Hz, $PhCH_2$), 4.57-4.42 (m, 10 H, $PhCH_2$ × 5), 4.40 (d, 1 H, J = 12.3 Hz, $PhCH_2$), 4.35-4.32 (m, 1 H, H-3'), 4.31 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.26 (br, 1 H, H-2"), 4.21-4.15 (m, 2 H, H-4', H-5'), 4.10 (dd, 1 H, J = 3.0, 2.8 Hz, H-4"), 4.06 (dd, 1 H, J = 7.1, 3.0 Hz, H-4), 4.05-3.99 (m, 3 H, H-2', H-5", H-3), 3.96-3.94 (m, 1 H, H-2), 3.90 (dd, 1 H, J = 10.5, 4.0 Hz, H-6), 3.86-3.73 (m, 5 H, H-3", H-6" × 2, H-5, H-6'), 3.70-3.64 (m, 2 H, H-6, H-6'), 3.33 (s, 3 H, OCH_3), 1.35 (s, 3 H, isopropylidene CH_3), 1.33 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.52 (Ar), 138.48 (Ar), 138.15 (Ar), 137.87 (Ar×2), 137.76 (Ar), 137.72 (Ar), 128.36 (Ar), 128.33 (Ar), 128.31 (Ar), 128.26 (Ar), 128.22 (Ar), 128.17 (Ar), 128.15 (Ar), 128.12 (Ar), 128.08 (Ar), 127.96 (Ar), 127.90 (Ar), 127.80 (Ar), 127.79 (Ar), 127.78 (Ar), 127.73 (Ar), 127.70 (Ar), 127.67 (Ar), 127.62 (Ar), 127.55 (Ar), 127.48 (Ar), 127.44 (Ar), 109.72 (isopropylidene C), 108.98 (C-1"), 107.00 (C-1), 106.66 (C-1'), 88.59 (C-3), 88.35 (C-2), 85.54 (C-3"), 82.94 (C-2', C-3'), 82.44 (C-4"), 80.96 (C-4), 80.60 (C-4'), 78.00 (C-2"), 76.46 (C-5), 76.37 (C-5"), 73.52 ($PhCH_2$), 73.40 ($PhCH_2$), 73.12 (C-5'), 72.19 ($PhCH_2$), 72.15 ($PhCH_2$), 71.86 ($PhCH_2$), 71.84 ($PhCH_2$), 71.77 ($PhCH_2$), 71.02 (C-6'), 68.84 (C-6),

65.49 (C-6"), 54.68 (OCH_3), 25.77 (isopropylidene CH_3), 25.72 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{71}H_{80}O_{16}Na$ 1211.5339, found 1211.5338.

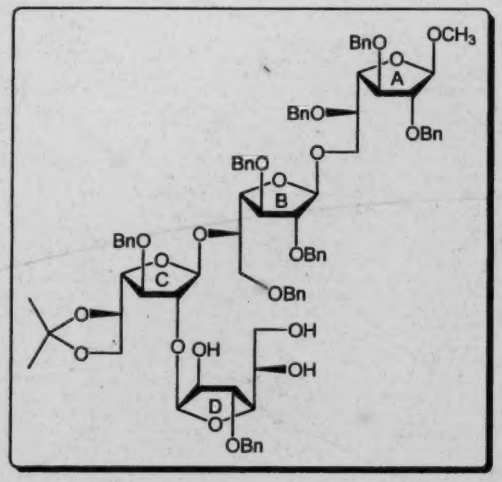
Methyl 2,3,5-tri-*O*-benzyl-6-*O*-{2,3,6-tri-*O*-benzyl-5-*O*-[3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-(2,3-anhydro-5,6-di-*O*-benzoyl-α-D-gulofuranosyl)-β-D-galactofuranosyl]-β-D-galactofuranosyl}-β-D-galactofuranoside (97).



Glycosylation of donor **6** (381 mg, 0.77 mmol) and compound **96** (368 mg, 0.31 mmol) was carried out following the general protocol for glycosylation of sulfoxide, and the reaction mixture was stirred for 24 h before workup. The pure compound **97** (359 mg, 75%) was isolated by chromatography (3:1, hexanes:EtOAc) as a colorless syrup. R_f 0.47 (2:1, hexanes:EtOAc); $[\alpha]_D$ –29.3 (*c* 1.45, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.20-7.98 (m, 4 H, Ar), 7.58-7.50 (m, 2 H, Ar), 7.45-7.17 (m, 39 H, Ar), 5.72 (ddd, 1 H, J = 5.8, 5.8, 4.1 Hz, H-5d), 5.42 (s, 1 H, H-1c), 5.11 (s, 1 H, H-1b), 5.05 (s, 1 H, H-1d), 4.94 (s, 1 H, H-1a), 4.77-4.65 (m, 5 H, $PhCH_2$ × 1.5, H-6d × 2), 4.58-4.38 (m, 11 H, $PhCH_2$ × 5, H-2c), 4.30 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.27 (dd, 1 H, J = 7.0, 3.2 Hz, H-3b), 4.23 (ddd, 1 H, J = 9.2, 2.7, 2.7 Hz, H-5b), 4.19 (dd, 1 H, J = 7.3, 7.3 Hz, H-4c), 4.11-4.04 (m, 4 H, H-4b, H-5c, H-4a, H-4d), 4.03-4.00 (m, 2 H, H-2b, H-3a), 3.97-3.95 (m, 1 H, H-2a), 3.90 (dd, 1 H, J = 10.3, 4.0 Hz,

H-6a), 3.85 (dd, 1 H, J = 9.8, 9.2 Hz, H-6b), 3.80 (dd, 1 H, J = 7.3, 3.5 Hz, H-3c), 3.79-3.75 (m, 2 H, H-5a, H-6c), 3.71-3.65 (m, 2 H, H-6a, H-6c), 3.64 (dd, 1 H, J = 9.8, 2.7 Hz, H-6b), 3.56 (d, 1 H, J = 2.9 Hz, H-3d), 3.32 (s, 3 H, OCH_3), 3.10 (d, 1 H, J = 2.9 Hz, H-2d), 1.26 (s, 3 H, isopropylidene CH_3), 1.24 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.01 (C=O), 165.76 (C=O), 138.43 (Ar × 2), 138.31 (Ar), 137.83 (Ar), 137.70 (Ar), 137.62 (Ar), 137.39 (Ar), 133.16 (Ar), 133.13 (Ar), 129.83 (Ar), 129.70 (Ar), 129.66 (Ar), 128.44 (Ar), 128.39 (Ar), 128.33 (Ar), 128.30 (Ar), 128.25 (Ar), 128.22 (Ar), 128.19 (Ar), 127.99 (Ar), 127.91 (Ar), 127.82 (Ar), 127.76 (Ar), 127.74 (Ar), 127.70 (Ar), 127.63 (Ar), 127.58 (Ar), 127.55 (Ar), 127.50 (Ar), 127.48 (Ar), 109.41 (isopropylidene C), 108.18 (C-1c), 107.01 (C-1a), 106.66 (C-1b), 100.56 (C-1d), 88.26 (C-2a, C-3a), 87.72 (C-2c), 83.88 (C-3b), 83.18 (C-3c), 82.84 (C-2b), 81.80 (C-4c), 81.11 (C-4a), 80.94 (C-4b), 76.20 (C-5a, C-5c), 75.18 (C-4d), 74.85 (C-5b), 73.54 (Ph$\underline{C}H_2$), 73.32 (Ph$\underline{C}H_2$), 72.59 (Ph$\underline{C}H_2$), 72.16 (Ph$\underline{C}H_2$), 71.81 (Ph$\underline{C}H_2$), 71.79 (Ph$\underline{C}H_2$ × 2), 71.74 (C-6b), 71.62 (C-5d), 68.68 (C-6a), 65.34 (C-6c), 63.36 (C-6d), 55.25 (C-2d), 54.74 (OCH_3), 54.31 (C-3d), 26.44 (isopropylidene CH_3), 25.55 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{91}H_{96}O_{22}Na$ 1563.6291, found 1563.6305.

Methyl 2,3,5-tri-*O*-benzyl-6-*O*-{2,3,6-tri-*O*-benzyl-5-*O*-[3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-(3-*O*-benzyl-α-D-galactofuranosyl)-β-D-galactofuranosyl]-β-D-galactofuranosyl}-β-D-galactofuranoside (98).

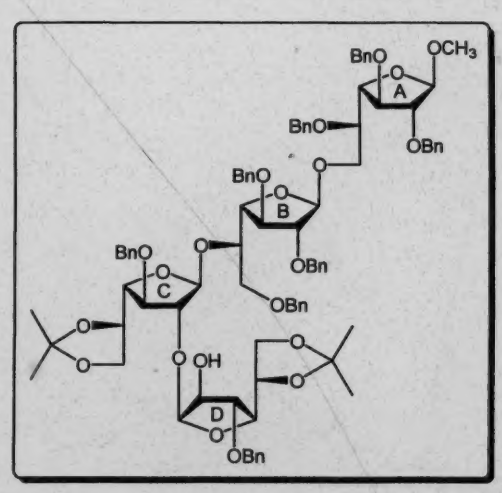


Compound **97** (60 mg, 0.039 mmol) was subjected to the general protocol to open the epoxide ring, and the resulting residue was purified by chromatography (1:1, hexanes: EtOAc) to give **98** (80 mg, 65%) as a colorless syrup. R_f 0.41 (1:1, hexanes: EtOAc); $[\alpha]_D$ –36.7 (*c* 2.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.37-7.20 (m, 40 H, Ar), 5.41 (s, 1 H, H-1c), 5.11 (d, 1 H, *J* = 4.8 Hz, H-1d), 5.10 (s, 1 H, H-1b), 4.94 (s, 1 H, H-1a), 4.79 (d, 1 H, *J* = 11.8 Hz, $PhCH_2$), 4.73 (d, 1 H, *J* = 11.8 Hz, $PhCH_2$), 4.67 (d, 1 H, *J* = 11.7 Hz, $PhCH_2$), 4.60-4.39 (m, 13 H, $PhCH_2$ × 6, H-2c), 4.30 (d, 1 H, *J* = 11.7 Hz, $PhCH_2$), 4.24 (dd, 1 H, *J* = 7.1, 3.2 Hz, H-3b), 4.19-4.14 (m, 2 H, H-4c, H-5b), 4.11-4.07 (m, 2 H, H-4b, H-5c), 4.07 (dd, 1 H, *J* = 7.2, 3.3 Hz, H-4a), 4.03 (dd, 1 H, *J* = 6.3, 3.0 Hz, H-3c), 4.02-3.91 (m, 6 H, H-3a, H-2b, H-3d, H-4d, H-2a, H-2d), 3.89 (dd, 1 H, *J* = 10.3, 4.2 Hz, H-6a), 3.80-3.74 (m, 4 H, H-6c × 2, H-5a, H-6b), 3.67 (dd, 1 H, *J* = 10.3, 7.7 Hz, H-6a), 3.66-3.62 (m, 1 H, H-5d), 3.61 (dd, 1 H, *J* = 10.2, 3.2 Hz, H-6b), 3.59-3.57 (m, 2 H, H-6d × 2), 3.31 (s, 3 H, OCH_3), 2.74 (br, 1 H, OH), 2.56 (br, 1 H, OH), 1.33 (s, 3 H, isopropylidene CH_3), 1.31 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.42 (Ar), 138.21 (Ar), 137.91

(Ar), 137.81 (Ar), 137.67 (Ar × 2), 137.57 (Ar × 2), 128.47 (Ar), 128.46 (Ar), 128.40 (Ar), 128.39 (Ar), 128.33 (Ar), 128.29 (Ar), 128.25 (Ar), 128.14 (Ar), 128.00 (Ar), 127.90 (Ar), 127.84 (Ar), 127.83 (Ar), 127.81 (Ar), 127.77 (Ar), 127.75 (Ar), 127.72 (Ar), 127.66 (Ar), 127.60 (Ar), 127.55 (Ar), 109.64 (isopropylidene C), 107.00 (C-1a), 106.86 (C-1c), 106.63 (C-1b), 101.69 (C-1d), 88.25 (C-2a), 88.22 (C-3a), 86.76 (C-2c), 83.69 (C-3b), 83.65 (C-3c), 82.84 (C-2b), 82.81 (C-3d), 82.28 (C-4a), 81.41 (C-4c), 80.99 (C-4b), 80.90 (C-5c), 77.18 (C-2d), 76.24 (C-5a), 75.78 (C-4d), 74.77 (C-5b), 73.55 ($PhCH_2$), 73.41 ($PhCH_2$), 72.39 ($PhCH_2$), 72.15 ($PhCH_2$), 72.14 ($PhCH_2$), 72.05 (C-5d), 71.95 ($PhCH_2$ × 2), 71.88 ($PhCH_2$), 71.82 (C-6b), 68.72 (C-6a), 65.44 (C-6c), 64.09 (C-6d), 54.74 (OCH_3), 26.12 (isopropylidene CH_3), 25.41 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{84}H_{96}O_{21}Na$ 1463.6342, found 1463.6345.

Methyl 2,3,5-tri-*O*-benzyl-6-*O*-{2,3,6-tri-*O*-benzyl-5-*O*-[3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-(3-*O*-benzyl-5,6-*O*-isopropylidene-α-D-galactofuranosyl)-β-D-galactofuranosyl]-β-D-galactofuranosyl}-β-D-galactofuranoside (99).

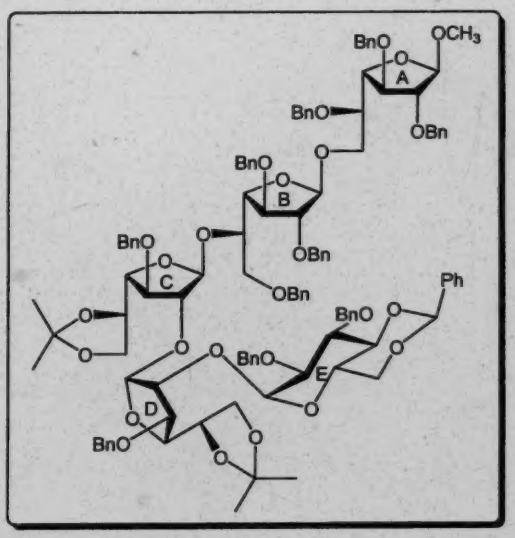
To a solution of compound **98** (160 mg, 0.11 mmol) and 2,2-dimethoxypropane (0.11 mL, 0.89 mmol) in dry acetone (5 mL) was added cat. *p*-TsOH (0.5 mg) and the reaction mixture was stirred at room temperature for 4 h. Two drops of triethylamine was added and the reaction mixture was concentrated. Column chromatography (3:1, hexanes:EtOAc) of the residue gave the tetrasaccharide **99** (145 mg, 88%) as a colorless oil. R_f 0.51 (2:1, hexanes:EtOAc); $[\alpha]_D$ –36.8 (*c* 0.6, CH_2Cl_2); ^1H NMR (500 MHz,



$CDCl_3$, δ_H) 7.40-7.20 (m, 40 H, Ar), 5.42 (s, 1 H, H-1c), 5.12 (d, 1 H, J = 4.8 Hz, H-1d), 5.09 (s, 1 H, H-1b), 4.95 (s, 1 H, H-1a), 4.80 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.79 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.74 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.61 (d, 1 H, J = 11.2 Hz, $PhCH_2$), 4.60-4.58 (m, 1 H, H-2c), 4.58-4.43 (m, 10 H, $PhCH_2$ × 5), 4.40 (d, 1 H, J = 11.2 Hz, $PhCH_2$), 4.31 (d, 1 H, J = 11.7 Hz, $PhCH_2$), 4.23 (dd, 1 H, J = 6.9, 3.5 Hz, H-3b), 4.20-4.06 (m, 6 H, H-4c, H-5b, H-4b, H-5c, H-4a, H-4d), 4.02-3.99 (m, 2 H, H-3a, H-2b), 3.97-3.64 (m, 14 H, H-3c, H-2a, H-2d, H-3d, H-5a, H-5d, H-6a × 2, H-6c × 2, H-6b × 2, H-6d × 2), 3.33 (s, 3 H, OCH_3), 2.60 (br, 1 H, OH), 1.41 (s, 3 H, isopropylidene CH_3), 1.31 (s, 3 H, isopropylidene CH_3), 1.29 (s, 3 H, isopropylidene CH_3), 1.26 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.46 (Ar), 138.31 (Ar), 138.04 (Ar), 137.84 (Ar), 137.77 (Ar), 137.71 (Ar), 137.65 (Ar), 137.50 (Ar), 128.46 (Ar), 128.43 (Ar), 128.39 (Ar), 128.33 (Ar), 128.31 (Ar), 128.27 (Ar), 128.25 (Ar), 128.17 (Ar), 128.05 (Ar), 128.00 (Ar), 127.95 (Ar), 127.83 (Ar), 127.79 (Ar), 127.77 (Ar), 127.74 (Ar), 127.68 (Ar), 127.66 (Ar), 127.53 (Ar), 109.78 (isopropylidene C), 109.56 (isopropylidene C), 107.31 (C-1c), 106.98 (C-1a), 106.66 (C-1b), 101.86 (C-1d), 88.29 (C-3c, C-2b), 86.28 (C-2c), 84.41 (C-2a), 83.57 (C-3b), 83.30, 82.86 (C-3a), 82.32, 81.97, 81.11, 80.92, 78.38 (C-5c), 76.34 (C-2d), 76.24 (× 2), 74.73, 73.54 ($PhCH_2$), 73.39 ($PhCH_2$), 72.42 ($PhCH_2$), 72.24 ($PhCH_2$), 72.15 ($PhCH_2$),

72.00 (C-6b), 71.81 ($PhCH_2$ × 2), 71.58 (Bn CH_2), 68.76 (C-6a), 65.51 (C-6c), 65.22 (C-6d), 54.74 (OCH_3), 26.69 (isopropylidene CH_3), 26.27 (isopropylidene CH_3), 25.64 (isopropylidene CH_3), 25.52 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{87}H_{100}O_{21}Na$ 1503.6655, found 1503.6651.

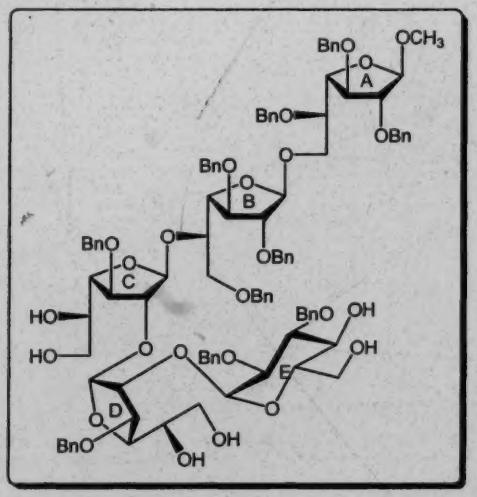
Methyl 2,3,5-tri-*O*-benzyl-6-*O*-{2,3,6-tri-*O*-benzyl-5-*O*-[3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-(3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-(4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranosyl)-α-D-galactofuranosyl)-β-D-galactofuranosyl]-β-D-galactofuranosyl}-β-D-galactofuranoside (103).



The glycosylation of donor **84** (140 mg, 0.25 mmol) and compound **99** (75 mg, 0.051 mmol) was carried out following the general protocol for glycosylation of thioglycoside with BSP/Tf_2O, and the reaction mixture was stirred for 48 h at room temperature before workup. The pure compound **103** (54 mg, 56%) was isolated by chromatography (7:3, hexanes:EtOAc) as a colorless syrup. R_f 0.47 (7:3, hexanes:EtOAc); $[\alpha]_D$ –2.7 (*c* 1.4, CH_2Cl_2); ^1H NMR (600 MHz, CD_2Cl_2, δ_H) 7.50-7.21 (m, 55 H, Ar), 5.57 (s, 1 H, benzylidene CH), 5.44 (d, 1 H, J = 1.2 Hz, H-1c), 5.40 (d, 1 H, J = 4.2 Hz, H-1d), 5.11 (d, 1 H, J = 3.6 Hz, H-1e), 5.09 (s, 1 H, H-1b), 4.89 (s, 1 H, H-1a), 4.86-4.79 (m, 4 H,

$PhCH_2$ × 2), 4.71 (d, 1 H, J = 11.5 Hz, $PhCH_2$), 4.69 (d, 1 H, J = 11.5 Hz, $PhCH_2$), 4.63-4.34 (m, 15 H), 4.27 (dd, 1 H, J = 7.5, 4.2 Hz, H-2d), 4.21 (dd, 1 H, J = 10.2, 4.7 Hz), 4.19 (dd, 1 H, J = 7.0, 3.2 Hz, H-3b), 4.17-4.12 (m, 4 H), 4.05-3.97 (m, 5 H), 3.93-3.92 (m, 1 H, H-2a), 3.90-3.82 (m, 5 H), 3.81-3.61 (m, 9 H), 3.58-3.54 (m, 2 H), 3.28 (s, 3 H, OCH_3), 1.38 (s, 3 H, isopropylidene CH_3), 1.19 (s, 3 H, isopropylidene CH_3), 1.17 (s, 3 H, isopropylidene CH_3), 1.16 (s, 3 H, isopropylidene CH_3); ^{13}C NMR (125 MHz, CD_2Cl_2, δ_C) 139.23 (Ar), 139.12 (Ar), 138.89 (Ar), 138.79 (Ar), 138.64 (Ar), 138.40 (Ar), 138.26 (Ar×2), 138.19 (Ar), 138.06 (Ar), 137.48 (Ar), 129.25 (Ar), 129.17 (Ar), 128.85 (Ar), 128.78 (Ar), 128.75 (Ar), 128.74 (Ar), 128.67 (Ar), 128.64 (Ar), 128.58 (Ar), 128.54 (Ar), 128.49(Ar), 128.44(Ar), 128.37 (Ar), 128.35 (Ar), 128.33 (Ar), 128.29 (Ar), 128.26 (Ar), 128.21 (Ar), 128.17 (Ar), 128.12 (Ar), 128.08 (Ar), 128.02 (Ar), 127.95 (Ar), 127.83 (Ar), 127.80 (Ar), 127.77 (Ar), 126.57 (Ar), 110.00 (isopropylidene C), 109.63 (isopropylidene C), 107.32 (C-1a), 107.25 (C-1c), 107.01 (C-1b), 101.75 (benzylidene CH), 99.07 (C-1d), 95.66 (C-1e), 88.67 (× 2), 85.68, 84.73, 84.32, 83.56, 82.11, 81.72, 81.68, 81.58, 81.48, 80.79, 79.10, 79.02 (× 2), 77.99, 77.13, 76.89, 75.46, 75.20, 73.70, 73.64, 73.29, 72.94, 72.80, 72.56, 72.51, 72.18 (× 3), 69.19, 68.64, 65.53, 65.47, 63.99, 54.82 (OCH_3), 26.95 (isopropylidene CH_3), 26.62 (isopropylidene CH_3), 25.66 (isopropylidene CH_3), 25.63 (isopropylidene CH_3). HRMS (ESI) calcd. for (M+Na) $C_{114}H_{126}O_{26}Na$ 1933.8435, found 1933.8449.

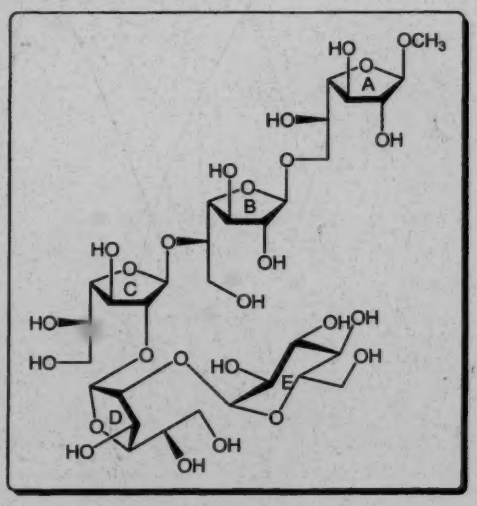
Methyl 2,3,5-tri-*O*-benzyl-6-*O*-{2,3,6-tri-*O*-benzyl-5-*O*-[3-*O*-benzyl-2-*O*-(3-*O*-benzyl-2-O-(2,3-di-*O*-benzyl-α-D-glucopyranosyl)-α-D-galactofuranosyl)-β-D-galactofuranosyl]-β-D-galactofuranosyl}-β-D-galactofuranoside (104).



A solution of **103** (40 mg, 0.02 mmol) in 70% HOAc (7 mL, HOAc:H_2O:THF 5:1:1) was stirred at 50 °C for 16 h. The resulting mixture was concentrated and purified by chromatography (30:1, CH_2Cl_2: CH_3OH) to give **104** (28.1 mg, 77%) as a colorless syrup. R_f 0.36 (20:1, CH_2Cl_2:CH_3OH); $[\alpha]_D$ –5.07 (*c* 0.15, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$, δ_H) 7.39-7.20 (m, 50 H, Ar), 5.44 (s, 1 H, H-1c), 5.20 (d, 1 H, J = 4.3 Hz, H-1d), 5.06 (d, 1 H, J = 1.0 Hz, H-1b), 5.00 (d, 1 H, J = 3.3 Hz, H-1e), 4.96 (d, 1 H, J = 11.3 Hz, $PhCH_2$), 4.92 (br s, 1 H, H-1a), 4.74-4.67 (m, 4 H, $PhCH_2$ × 2), 4.63 (d, 1 H, J = 11.9 Hz, $PhCH_2$), 4.59 (d, 1 H, J = 11.3 Hz, $PhCH_2$), 4.55-4.38 (m, 13 H), 4.34 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.29 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.22 (dd, 1 H, J = 5.9, 2.5 Hz, H-4c), 4.14 (dd, 1 H, J = 5.9, 2.4 Hz, H-3c), 4.11-4.04 (m, 5 H), 4.00-3.98 (m, 2 H), 3.97 (dd, 1 H, J = 3.1, 1.0 Hz, H-2b), 3.90 (dd, 1 H, J = 3.2, 1.3 Hz, H-2a), 3.87 (dd, 1 H, J = 10.2, 4.0 Hz), 3.83 (dd, 1 H, J = 9.2, 9.2 Hz), 3.78-3.70 (m, 3 H), 3.69-3.46 (m, 10 H), 3.44-3.39 (m, 2 H), 3.28 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.65 (Ar), 138.38 (Ar), 137.97 (Ar), 137.89 (Ar × 2), 137.77 (Ar), 137.69 (Ar), 137.65 (Ar), 137.54 (Ar), 137.33 (Ar), 128.52 (Ar), 128.45

(Ar), 128.38 (Ar), 128.32 (Ar), 128.24 (Ar), 128.12 (Ar), 128.00 (Ar), 127.98 (Ar), 127.83 (Ar), 127.77 (Ar), 127.74 (Ar), 127.65 (Ar), 127.60 (Ar), 107.00 (C-1a), 106.45 (C-1c), 106.41 (C-1b), 99.93 (C-1d), 95.89 (C-1e), 88.23 (× 2), 87.79, 85.32, 83.73, 83.45, 82.87, 82.77, 82.52, 80.78 (× 4), 80.26, 78.98, 76.19 (× 2), 75.41, 75.13, 73.52, 73.41, 72.95, 72.27, 72.13 (× 2), 72.03, 71.92, 71.82, 71.34, 70.96, 70.57, 68.54, 64.38, 64.15, 62.46, 54.74 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{101}H_{114}O_{26}Na$ 1765.7496, found 1765.7509.

Methyl 6-*O*-{5-*O*-[2-*O*-(2-O-(α-D-glucopyranosyl)-α-D-galactofuranosyl)-β-D-galacto -furanosyl]-β-D-galactofuranosyl}-β-D-galactofuranoside (67).



To a solution of compound **104** (14 mg, 0.008 mmol) in CH_3OH (2 mL) was added 20% $Pd(OH)_2$ on carbon (5 mg) and the reaction mixture was stirred under hydrogen atmosphere for 24 h. The mixture was filtered through Celite and concentrated to yield compound **67** (6.8 mg, 100%) as a white foam. R_f 0.53 (100% CH_3OH); $[\alpha]_D$ +1.9 (*c* 0.52, H_2O); ^1H NMR (600 MHz, D_2O, δ_H) 5.37 (d, 1 H, J = 4.3 Hz, H-1d), 5.32 (s, 1 H, H-1c), 5.01 (s, 1 H, H-1b), 4.99 (d, 1 H, J = 3.6 Hz, H-1e), 4.91 (s, 1 H, H-1a), 4.36 (dd, 1 H, J = 8.0, 7.9 Hz), 4.28-4.22 (m, 3 H), 4.13-4.10 (m, 2 H), 4.09-4.04 (m, 4 H), 3.99-3.93 (m, 3 H), 3.88-3.60 (m, 15 H), 3.55 (dd, 1 H, J = 10.0, 3.7

Hz), 3.44 (dd, 1 H, J = 9.6, 9.4 Hz), 3.41 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, D_2O, δ_C) 108.99 (C-1a), 108.63 (C-1b), 106.67 (C-1c), 99.66 (C-1d), 98.18 (C-1e), 87.80, 83.90, 82.66, 82.30, 81.93 (× 2), 81.64, 80.55, 77.58, 77.55, 77.14, 75.61, 73.66, 73.37, 73.34, 72.90, 72.12, 70.98, 70.49, 70.32, 69.95, 63.72, 63.13, 62.33, 61.30, 55.79 (OCH_3). HRMS (ESI) calcd. for (M+Na) $C_{31}H_{54}O_{26}Na$ 865.2796, found 865.2795.

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